

UNIVERSITY OF KWAZULU-NATAL

**ORGANOCATALYZED SYNTHESIS OF
CARBAPENEM β -LACTAM CORES AND
MONOBACTAM**

2014

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2014

A thesis submitted to the School of Health Sciences, Faculty of Health Science, University of KwaZulu-Natal, Westville, for the degree of Master of Pharmaceutical Chemistry.

This is a thesis in which the chapters are written as a set of discrete research papers, with an overall Introduction and final Discussion. Typically these chapters will have been published in internationally recognized, peer-reviewed journals.

As the candidate's supervisors, we have approved this thesis for submission.

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Abstract

Organocatalysis has emerged as a new powerful methodology for the catalytic production of enantiomerically pure organic compounds. The main aim of this work was to develop organocatalyzed routes to novel β -lactam derivatives. In chapter 2, the first organocatalyzed C-C bond forming reactions have been performed on the carbapenem core **1**, was the Aldol reaction, with various aldehydes to afford the corresponding products in good yields (up to 76%) and excellent diastereoselectivities (up to 99:1 ratios). Next, the Mannich reaction was evaluated with different amines and aldehydes. The products were obtained with modest chemical efficiency (up to 55%) and excellent diastereoselectivities (up to 99:1 ratios) as with the Aldol reaction. The reactivity of the carbapenem core **1** was also evaluated in the Michael addition reaction with electrophilic olefins. Chapter 3 includes the full substrate scope of organocatalytic asymmetric Michael addition transformations on the carbapenem core **1** reported. Good yields (up to 67%) and some excellent diastereoselectivities (up to 92:8 ratios) were obtained with L-proline as the organocatalyst. We have also demonstrated the possibility to effectively convert the Michael products to monobactams through a retro-Dieckmann reaction under basic conditions, thereby leading to another highly valued class of β -lactam antibiotics. Chapter 4 is the summary of the thesis.

DECLARATIONS

DECLARATION 1 – PLAGIARISM

I, **Sibusiso Khanyase** declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.
2. This thesis has not been submitted for any degree or examination at any other university.
3. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
4. This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
 - a. Their words have been re-written but the general information attributed to them has been referenced
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DECLARATION 2 – PUBLICATIONS

DETAILS OF CONTRIBUTION TO PUBLICATIONS that form part and/or include research presented in this thesis (include publications in preparation, submitted, *in press* and published and give details of the contributions of each author to the experimental work and writing of each publication)

List of publications

1. S. A. Pawar, S. Alapour, S. Khanyase, Z. E. D. Cele, S. Chitti, H. G. Kruger, T. Govender, P. I. Arvidsson, *Org. Biomol. Chem.* **2013**, *11*, 8294-8297.

S. Khanyase contributed on the project by performing all laboratory work for the Michael reactions and writing the section.

2. Khanyase, S.; Naicker, T.; Maguire, G. E. M.; Kruger, H. G.; Arvidsson, P. I.; Govender, T. L-Proline Organocatalyzed Michael Synthesis of Monobactam and Carbapenem β -Lactam core *Tetrahedron Asymmetry* **2014**, DOI 10.1016/j.tetasy.2014.05.006

S. Khanyase contributed to the design of the project, synthesised and characterised all compounds. He also wrote the manuscript.

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CHAPTER 1

1.1 Introduction into Chirality

The concept of stereochemistry as an essential attribute of molecular structure dates back to the origin of modern organic chemistry a century ago.¹ At the heart of stereochemistry, chirality is the essence of a molecular structure being pioneered by the great work of scientists such as Herschel,² Biot³ and Pasteur.⁴ Chirality is a geometrical attribute. An object is chiral when it is not superimposable upon its mirror image and achiral when it is superimposable. Two commonplace examples of chiral objects are an individual's right and left hands (**Figure 1**) and a pair of counterclockwise and clockwise-threaded screws.

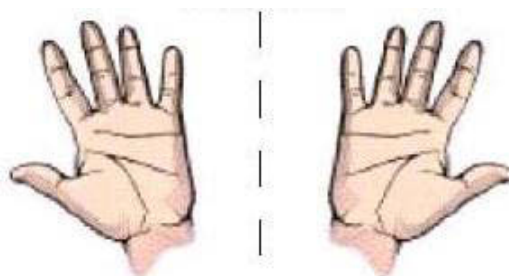


Figure 1: Example of enantiomers (left and right hand).⁵

Non-superimposable molecules are called enantiomers assigned as (*R*)- or (*S*)-enantiomers, they rotate plane-polarised light through equal angles but in opposite directions.⁶ Many of the compounds found in living organisms are chiral, for example enzymes, DNA and hormones. Therefore, the interaction of chiral compounds with these important building blocks in living organisms is unique.⁷ An example illustrating the differences are the enantiomers of dichlorprop; the (*R*)-(+)-dichlorprop is an active herbicide for killing the weeds, while the other (*S*)-(-)-dichlorprop enantiomer is inactive (**Figure 2**).⁸ Several other examples are found in literature.⁹ In conclusion, biology is very sensitive to chirality and the activity of the compounds also depends on which enantiomer is used.

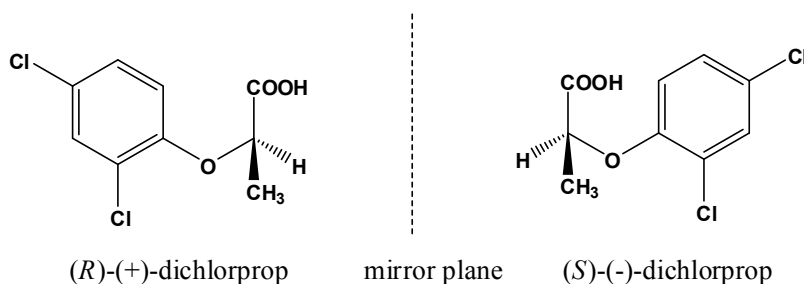


Figure 2: Enantiomers of dichlorprop

1.2 Routes to Obtain Enantiomerically Pure Compounds

There are three main synthetic approaches to obtain enantiopure compounds. These are mainly: resolution of racemates, chiral pool strategy and asymmetric synthesis. Next, the three main strategies are outlined.

1.2.1 Resolution of Racemates

The first optical resolution of a racemate mixture was performed by Pasteur, who was able to manually separate the two kinds of crystals from racemic tartaric acid salts.¹⁰ Resolution is the separation of an equimolar mixture of enantiomers.¹¹ This is achieved in three ways; (i) formation of diastereomers which are subsequently separated by chromatographic techniques and then converted back to individual enantiomers, (ii) discrimination of enantiomers by biological molecules such as enzymes and finally there is (iii) chiral chromatography in which the mixture is passed through a chiral column that has different affinity for the two enantiomers thus resulting in separation.^{6, 11-13} The major drawback in this approach is poor yields, only 50% of the desired enantiomer can be obtained unless any of the three approaches are further carried out.¹²

1.2.2 Chiral pool

The chiral pool synthesis utilizes naturally occurring enantiopure starting materials such as amino acids, carbohydrates, terpenes and carboxylic acids.¹⁴ This methodology is more useful when the desired final

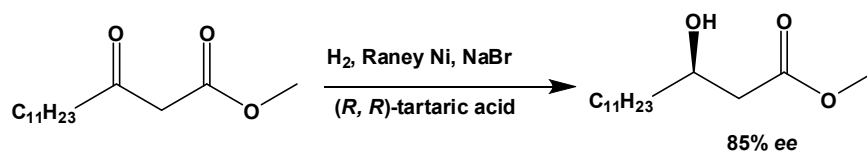
product resembles the enantiopure starting material. Otherwise long synthetic routes may be required resulting in lower yields.

1.2.3 Asymmetric Synthesis

Asymmetric synthesis involves the conversion of a prochiral substrates into a single enantiomer under the influence of a chiral molecule.¹⁵ It is an important method since it allows the synthesis of a variety of optically pure compounds. There are four basic strategies in asymmetric synthesis that will be further discussed.

1.2.3.1 Reagent Controlled

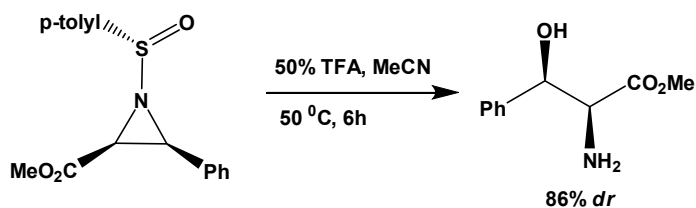
In this method, the reagent used is chiral and serves to direct the transformation of a prochiral substrate to an optically pure product.¹⁶ An example demonstrating the usefulness of this method was reported by Blakemore and co-workers in 2006, showing stereoselective conversion of ketoesters to alcohols using (*R, R*)-tartaric acid as a chiral reagent (**Scheme 1**).¹⁷



Scheme 1: Reagent controlled asymmetric synthesis (*ee* = enantiomeric excess)

1.2.3.2 Substrate Controlled

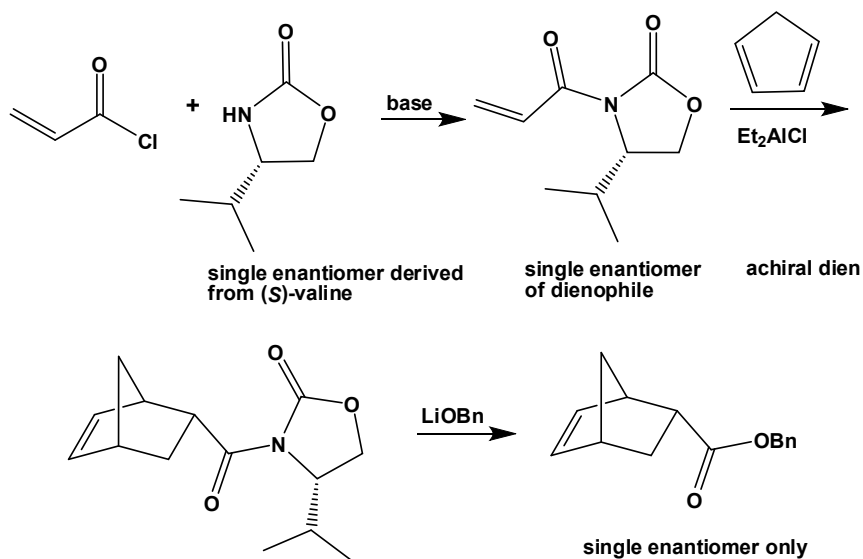
Substrate controlled asymmetric synthesis utilizes a chiral starting substrate which serves to control the introduction of new elements of chirality on the product.^{15, 16} David and co-workers were the first to report substrate-controlled asymmetric synthesis of α -amino acid derived from sulfinimine.¹⁸ They demonstrated the activating nature of the *p*-ST-sulfinyl group to promote ring opening of an aziridine ring in aqueous TFA to afford *syn*- β -phenylserine derivative in good selectivity (**Scheme 2**).



Scheme 2: Substrate controlled asymmetric synthesis (*dr* = diastereoselectivity).

1.2.3.3 Auxiliary-Controlled

Auxiliary-controlled asymmetric synthesis is based on the temporary incorporation of a chiral moiety in an achiral substrate generating new stereogenic centers. The process involves the introduction of the auxiliary which serves to direct the diastereoselective reaction, separation of the formed diastereoisomers and finally the recovery of the chiral auxiliary.^{15, 16} This method is not widely employed due to some drawbacks namely, the attachment and the recovery of the chiral reagent.¹⁹ An example illustrating this method is the chiral auxiliary-controlled Diels-Alder reaction which affords a single enantiomer of the product (**Scheme 3**).¹⁵



Scheme 3: Auxiliary controlled asymmetric synthesis.

1.2.3.4 Catalyst Controlled

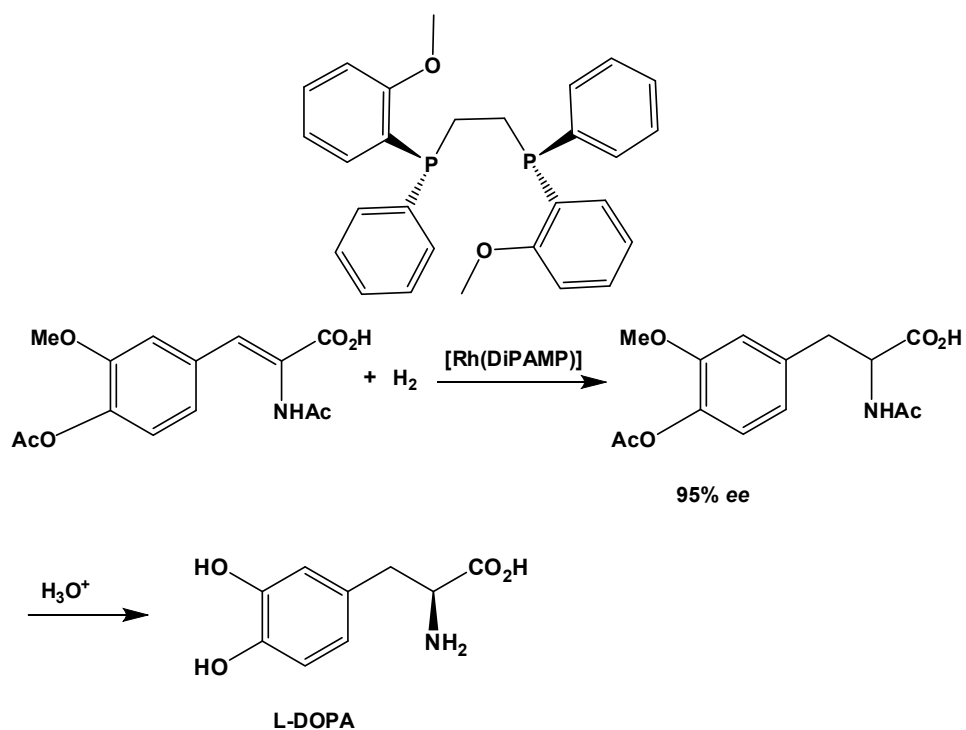
Catalyst-controlled asymmetric synthesis or asymmetric catalysis utilizes the chiral information from the catalyst which is transferred to an achiral substrate, converting it to an enantiopure product.^{11, 14} During the process, substoichiometric quantities of the catalyst are required to accelerate the reaction. The catalyst is not consumed and can be re-used in a new catalytic cycle.^{11, 14, 20, 21} This method will now be discussed in more details in the following section.

1.3 Asymmetric Catalysis

There are three main classes of asymmetric catalysts employed:

1.3.1 Metal-ligand Complexes as Catalysts

Organometallic catalysis is one of the most successful and widely used methods in asymmetric synthesis.^{11, 16, 22, 23} The success of this area of research is mostly due to the fact that metals have higher affinity to complex with structurally well-defined organic ligands which results in an efficient asymmetric induction. Much of what is known in this field of research has been pioneered by Knowles.²⁴ He demonstrated that complexes of rhodium and phosphine ligands, with C_2 symmetry, catalyzed the addition of hydrogen to one of the faces of a prochiral olefin to generate a stereogenic C-H center with high enantioselectivity. The success of this reaction led to an industrial preparation of L-DOPA (**Scheme 4**).¹⁶ As a drug, L-DOPA is used in the clinical treatment of Parkinson's disease and dopamine-responsive dystonia.²⁵

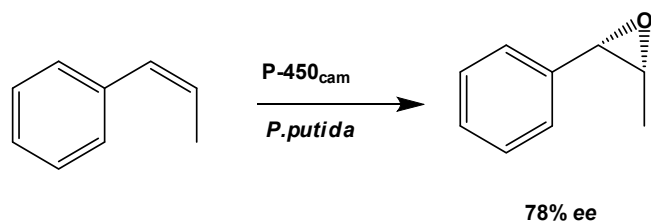


Scheme 4: Industrial preparation of L-DOPA using $[Rh(DIPAMP)]$ catalyst.

In spite of the success, some organometallic complexes are expensive and require strict reaction conditions.

1.3.2 Biocatalysts

Biocatalysis is the process where biomolecules such as enzymes are used to catalyze chemical reactions.^{26, 27} The advantage of using biocatalysts includes their high degree of regio-, and stereo-specificity under mild reaction conditions. An additional advantage of using biocatalysts includes reduced isomerization, racemization, epimerization and rearrangement effects that are common in organic synthesis.²⁸ However, there are some drawbacks with this methodology, namely their costs, some biocatalysts cannot be applied to a wide range of asymmetric reactions and therefore their use is limited in industry.²⁷ An example illustrating the use of biocatalysts was reported by Fruetel and co-workers on epoxidation of *cis*- β -methylstyrene using cytochrome P-450_{cam} from *Pseudomonas putida* (**Scheme 5**).²⁹



Scheme 5: Stereoselective epoxidation of *cis*- β -methylstyrene

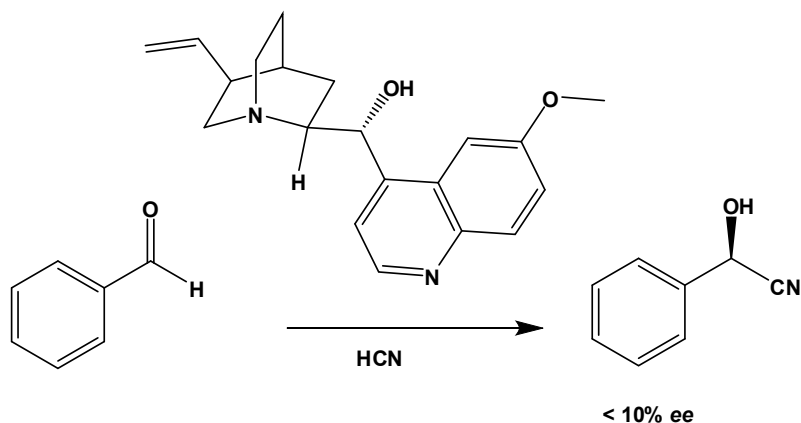
1.3.3 Organocatalysts

Asymmetric organocatalysis is defined as the acceleration of chemical reactions by small organic molecules in the absence of metals.^{30, 31} This is a new powerful method for the catalytic production of enantiomerically pure organic compounds and is one of the most rapidly growing research areas in synthetic chemistry.³⁰⁻³³

This method will be discussed in further details for the purpose of this project.

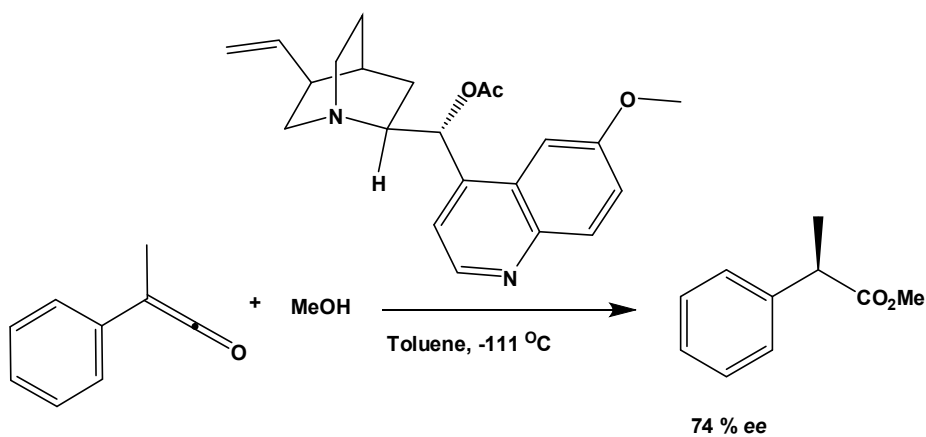
1.4 Asymmetric Organocatalysis

The use of small organic molecules to catalyze a chemical reaction has been known for over a century.³⁴ In 1896, Emil Knoevenagel used a secondary amine (piperidine) to catalyze the condensation reaction between diethylmalonate and benzaldehyde which resulted in the reaction being named after him that is the Knoevenagel condensation.³⁵ Mackwald in 1904 was the first to report asymmetric organocatalysis using the brucine alkaloid in a decarboxylation process.³⁶ In 1912, Bredig and Fiske described the asymmetric addition of HCN to benzaldehyde catalyzed by cinchona alkaloids with an *ee* of less than 10% for the reaction product (**Scheme 6**).³⁷



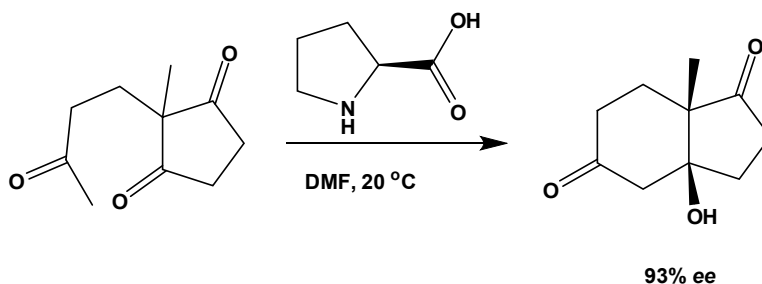
Scheme 6: Asymmetric addition of HCN to benzaldehyde catalyzed by cinchona alkaloids.

During the 1960's Pracejus published the organocatalytic methanolysis of a ketene with higher enantioselectivity (74 % *ee*) by using O-acetylquinine as the catalyst (**Scheme 7**).³⁸



Scheme 7: Organocatalytic methanolysis of a ketene by O-acetylquinine as the catalyst.

In the 1970s organocatalysis was revolutionized, when Hajos and Wiechert published the first asymmetric aldolization (Hajos-Parrish-Eder-Sauer-Wiechert reaction) catalyzed by L-proline with good enantioselectivity (**Scheme 8**).³⁹



Scheme 8: Hajos-Parrish-Eder-Sauer-Wiechert reaction.

In the late 1990s, things changed dramatically when Eric Jacobsen⁴⁰, Elias Corey⁴¹ and their co-workers, published the first examples of hydrogen-bonding catalysis, in an asymmetric Strecker reaction. However, the concept of organocatalysis wasn't fully described but it was demonstrated for the first time that small organocatalysts could be used effectively in chemical synthesis. In 2000, organocatalysis was effectively launched by two publications: one from Lerner, Barbas and List⁴² on enamine catalysis and the other by MacMillan⁴³ and co-workers on iminium catalysis. List demonstrated the ability of small molecules to catalyze reactions that were for long thought to only be promoted by larger molecules. The work by MacMillan represented the revival of the secondary amines and other small organic molecules as catalysts. The rapid growth in the field of organocatalysis was due to numerous advantages that small organic molecules possess such as; availability from naturally occurring materials, stability in aerobic environments as compared to metal-ligand catalysts which are mostly unstable, inexpensiveness and relatively easy to prepare, non-toxic nature and user friendly experimental setups.

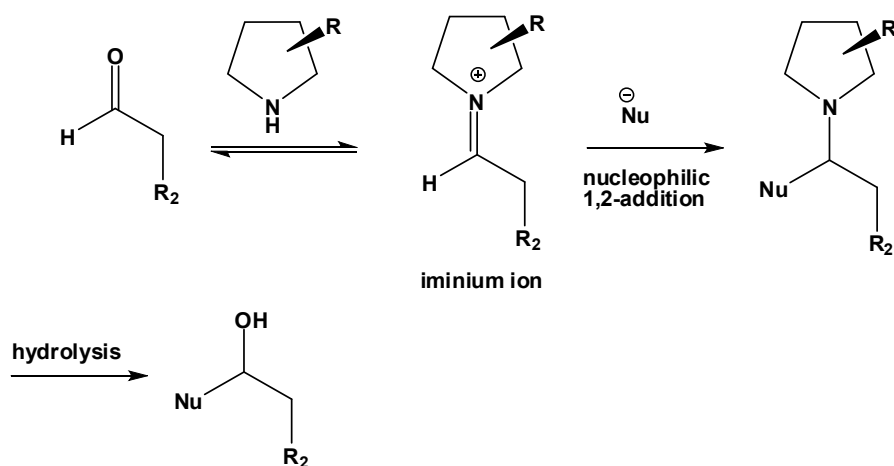
The most crucial aspect in the success of organocatalysis is the development of new activation methods. The different activation modes can be classified into covalent and non-covalent activation.

1.4.1 Covalent activation

Covalent activation is the process that involves the formation of covalent adducts between the catalyst and substrate within the catalytic cycle.³¹ Aminocatalysis in which interactions are covalent, make use of amines as catalysts and represents an important part of organocatalysis.^{30, 44-46} This can further be classified into the following list of classes.

1.4.1.1 Iminium Catalysis

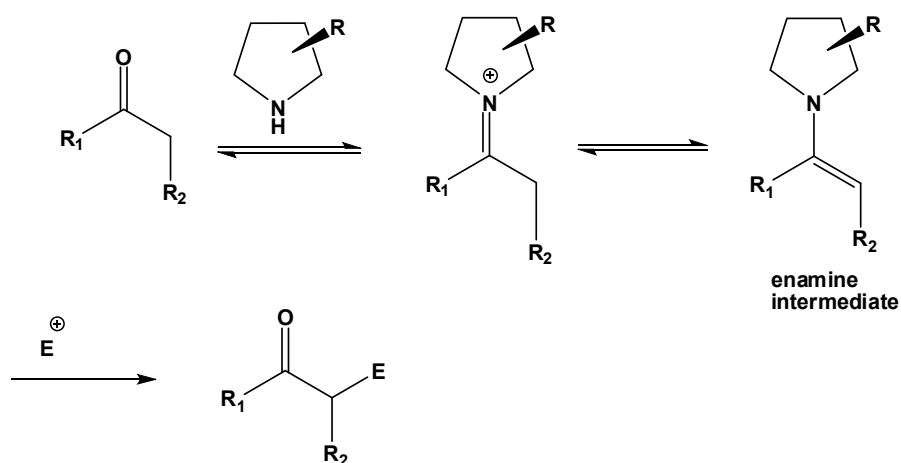
As already mentioned, the use of chiral secondary amines as catalysts to activate carbonyl compounds via the iminium catalysis was reported by MacMillan and co-workers. This was the first organocatalytic activation mode to be introduced as a general strategy for asymmetric synthesis.⁴³ Iminium catalysis is an alternative organocatalytic pathway to conventional Lewis acid catalysis of carbonyl compounds. The reactive species is an iminium ion formed by the condensation of a chiral amine with a carbonyl group (**Scheme 9**), resulting in lowering in the energy potential of the lowest unoccupied molecular orbital (LUMO) of the ionic intermediate and thus facilitating reactions with nucleophiles.^{46, 47}



Scheme 9: Activation via iminium ion ($\text{Nu} = \text{nucleophile}$)

1.4.1.2 Enamine Catalysis

Enamine catalysis involves the production of an enamine that results from the tautomerization of an iminium ion intermediate (**Scheme 10**).^{30, 45, 46, 48} It is essentially the activation by primary and secondary amines that facilitates electrophilic substitution reactions (typically) at the α -position of carbonyl containing compounds via highest occupied molecular orbital (HOMO) rising strategies.^{44, 45, 48, 49}



Scheme 10: Activation via enamine (E = electrophile).

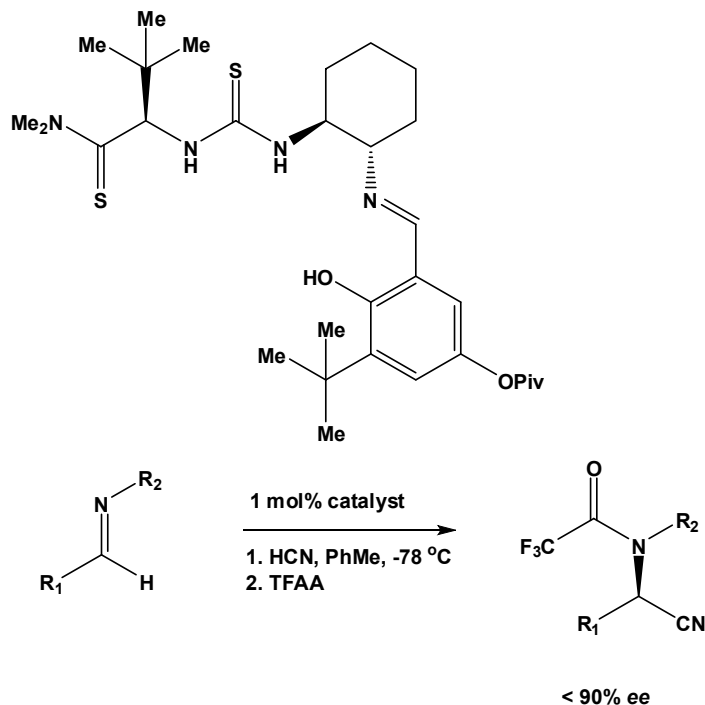
This strategy has been frequently used in Aldol, Mannich and Michael reactions.^{45, 50, 51} Enamine catalysis has recently been extended to dienamine catalysis,⁵² first introduced by Jorgensen and co-workers in 2006. It is used to activate the γ -position of α,β -unsaturated compounds rather than the α -position. Beyond the three strategies iminium, enamine and dienamine already mentioned, new pathways such as linear trienamine, cross-conjugated trienamine and vinylogous iminium-ion have been discovered.⁴⁴ These strategies allow the transfer of chiral information from the catalyst to reaction centers located at five to seven bonds away, which is of great importance for construction of structurally complex relevant molecules.

Apart from the above mentioned strategies, a new class of catalysis known as SOMO (single electron occupied molecular orbital) activation has also been developed.^{53, 54} In this method, a single electron occupied molecular orbital activation is produced allowing the introduction of different substituents in α -carbonyl positions. This method has merged organocatalysis with radical chemistry. Lastly, the catalysis via ammonium ion also uses amines as catalysts.^{55, 56} The formation of ammonium enolates mostly with cinchona alkaloids, and the formation of acyl-ammonium with DMAP analogues, are typical examples. Pracejus and Sauer reported the initial work exploiting this strategy on ketene dimerization reactions.^{57, 58} Since then, more groups have used this route to synthesize natural products such as siphonarienolone.⁵⁹⁻⁶¹

1.4.2 Non-Covalent Activation

Non-covalent activation is basically the formation of hydrogen-bonded adducts between the substrate and catalyst. Phase-transfer catalysis (PTC) by organic phase-transfer catalysts falls under this category. It is

performed in a heterogeneous medium and typically uses ammonium salts to facilitate the migration of the reagent from one phase to the other. The creation of chirality is based on the formation of a chiral ionic pair soluble in the organic phase where the stereoselective reaction occurs.^{30, 31, 62, 63} There are a range of reactions that are catalyzed by phase transfer molecules,⁶⁴ α,β -unsaturated ketone epoxidation can proceed using the Marouka catalysts.⁶⁵ Cinchona alkaloids have also shown to catalyze thiol conjugate addition to enones.⁶⁶ Lastly, hydrogen-bonding catalysis has been introduced as a powerful methodology for asymmetric catalysis. It has been known since the early 1980s,⁶⁷⁻⁶⁹ but better understood in the late 1990s complementary to Eric Jørgensen^{40, 70} and Elias Corey⁴¹ as previously mentioned. The ability to activate electrophiles with H-bonding is pivotal in hydrogen-bonding catalysis. Chiral diols such as Taddol were also used as H-donors to activate carbonyl compounds for cycloaddition reactions.⁷¹ Thiourea catalysts have been reported to selectively catalyze reactions such as the Strecker (Scheme 11),⁷² Mannich⁷⁰ and hydrophosphorylation.⁷³ Various other H-bonding catalysts have been reported to catalyze important reactions in chemical syntheses.³⁰



Scheme 11: Thiourea-catalyzed asymmetric Strecker reaction.

Asymmetric organocatalysis has been the forefront of research for a vast array of chemical transformations; aminocatalysis within the framework has shown to be a key pathway for the construction

of natural and unnatural significant molecules. Therefore, for this project aminocatalysis will be the main pathway for all transformations performed.

1.5 β -lactam Antibiotics

In 1912, the treatment of bacterial infections was revolutionized with the discovery of penicillin⁷⁴ and its subsequent synthesis by Sheehan and co-workers.⁷⁵⁻⁷⁷ Today, penicillin and all subclasses such as carbapenems bearing a β -lactam core structure (**Figure 2**) are the most widely used agents and represents about half of all antibacterial drugs.^{74, 78-80}

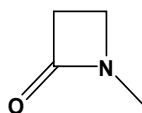


Figure 2: β -lactam core structure

Of the various β -lactams, the carbapenems subgroup possesses the broadest spectrum of activity and greatest potency against Gram-positive and negative bacteria. As a result, this class is often used as antibiotics of last resort for critically ill patients.^{79, 81-83} The recent emergence of multidrug-resistance (MDR) pathogens has seriously threatened the use of these agents.^{80, 83-85} Hence, this problem has prompted the search and development of additional facile routes to obtain unique derivatives on this pharmaceutically relevant skeleton.

There are several reported methods for the synthesis of β -lactams including named reactions as the classic Staudinger⁸⁶ as well as the Gilman-Speeter⁸⁷ and Kinugasa.⁸⁸ More recently organocatalysts have been employed in an effort to make the Staudinger reaction more efficient.⁸⁹ However, little work has been done in synthesizing β -lactams through organocatalysis. To bridge the gap, we envisaged the synthesis of β -lactam derivatives by utilizing organocatalytic methodologies.

1.6 Outline of this Thesis

The aim was to synthesize novel β -lactam derivatives through organocatalyzed (Aldol, Mannich and Michael) reactions. The carbapenem core **1** (**Figure 3**) is commonly used for the preparation of clinically used antibiotics.^{90, 91} We envisaged that this intermediate could be further substituted via HOMO-raising aminocatalysis,^{44, 45, 48, 49} thereby promoting reactions with electrophilic substrates.

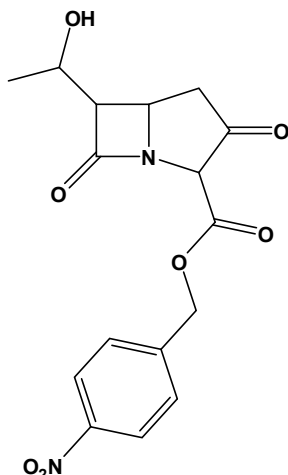


Figure 3: Carbapenem core **1**

Chapter **2** is the introductory results of the first amino catalyzed stereospecific C-C bond forming reactions on carbapenem core **1** through Aldol, Mannich and Michael reactions.

Chapter **3** is an expansion of the mild organocatalytic asymmetric Michael addition transformation on the carbapenem core **1**.

Chapter **4** is a summary of the work carried out for this project.

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CHAPTER 2

Organocatalyzed stereospecific C-C bond formation of β -lactams

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Abstract

Herein, we report the development of mild, organocatalyzed, routes to novel carbapenam derivatives through Aldol, Mannich and Michael C-C bond forming reactions.

Introduction

Compounds containing β -lactams (**Figure 1**) are amongst the most important molecules in clinical use today.¹⁻³ Most notably is their wide utility as antibacterial agents and as related β -lactamase inhibitors; however, β -lactams are also being explored in other therapeutic areas,⁴ including HIV protease inhibition.⁵ Given the global challenge of antibiotic resistance,⁶ there is an urgent need for increased focus on the discovery and development of antibacterial agents. Bacterial resistance may occur through a number of pathways, e.g. production of β -lactamases,⁷ efflux pumps, and mutations that alters expression and function of transpeptidase enzymes – the targets of most β -lactam antibiotics.^{8, 9} As β -lactams functions as both transpeptidase- and β -lactamase inhibitors much work is being direct to accessing novel

analogs of these critical molecular frameworks.¹⁰ However, the commercially viable synthesis of many β -lactams remains challenging due to a high degree of functionalization and chirality combined with the reactive nature of the core bicyclic ring-structures. Furthermore, most β -lactam antibiotics, except carbapenems and aztreonam, are being produced by biosynthetic routes rather than through chemical synthesis. Considering the challenges associated with synthetic modifications of the β -lactam framework, we envisioned that the mild conditions offered by organocatalysis might help overcome some of the limitations of current methodologies and open en-route to hitherto unexplored β -lactams.

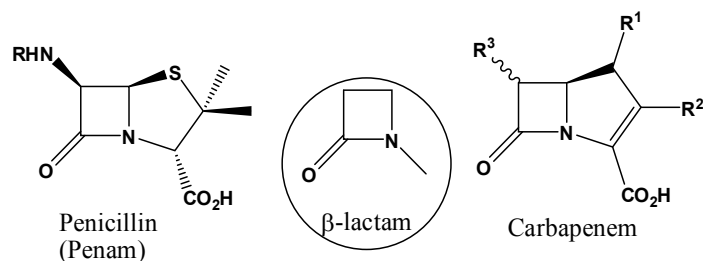
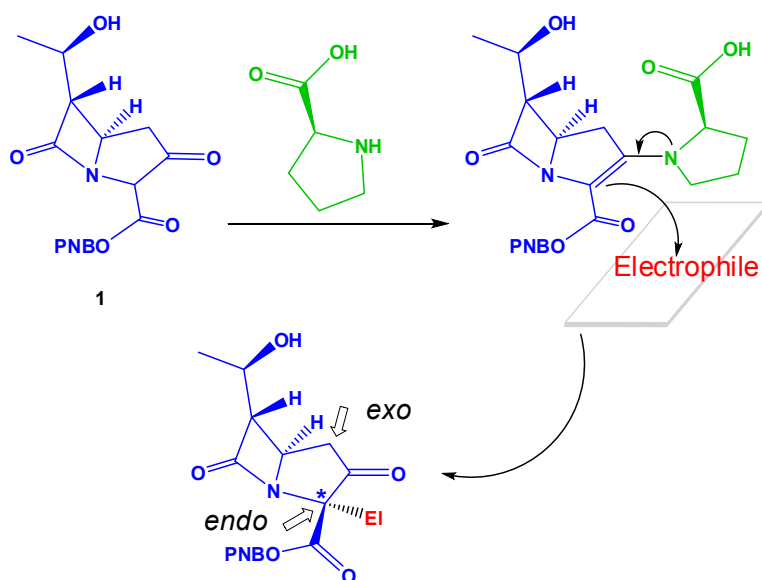


Figure 1: Examples of β -lactam antibiotics: Generic structure of penicillins with a saturated penam core and of synthetic carbapenems (e.g. Imipenem, Thienamycin, and Panipenem).

During the past decade, asymmetric organocatalysis¹¹⁻¹³ has grown extensively as a powerful tool in the construction of complex molecular skeletons in synthetic chemistry.¹⁴⁻¹⁹ Aldol,^{15, 20-24} Mannich^{15, 25, 26} and Michael^{15, 27, 28} reactions are some of the most powerful strategies in synthetic organic chemistry, since it allows the formation of new C-C bonds.²⁹

We envisaged that (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (1), the common intermediate for preparation of clinically used antibiotics Imipenem,³⁰ Thienamycin^{31, 32} and Panipenem,³³ could be further substituted via HOMO-raising amine catalysis,³⁴ thereby promoting reactions with electrophilic substrates (**Scheme 1**).



Scheme 1: Novel HOMO rising strategies offering a mild and facile route to carbapenam derivatives.

Results and Discussion

In order to test our hypothesis, we subjected the “carbapenam ketone” intermediate **1** to a reaction with the benchmark substrate formaldehyde as the electrophile, and Proline as the catalyst, Table 1. Various solvents such as DMF, DCM and THF were evaluated but no conversion was observed via LC-MS except when DMSO was employed (Table 1, entry 1). When the reactions were conducted with reagent grade DMSO as the solvent we observed the presence of product and a hydrolyzed form of the starting materials (+18 m/z on LC-MS). The use of dry DMSO resulted in no detection of the hydrolyzed starting material but also resulted in a slower and low yielding reaction. Acid additives are common additives in the organocatalyzed Aldol reactions,³⁵ so we next investigated the effect of formic and acetic acids. It was observed that there was no difference in reactivity or yields when acetic acid was used (Table 1, entry 2) whereas formic acid enhanced the hydrolysis side reaction. Under solvent free conditions, the rate of the reaction was improved significantly (Table 1, entry 3). D-Proline gave similar results as L-Proline with respect to reaction times and yields (Table 1, entries 1 and 4), but also with respect to the diastereomeric ratio of the product formed. This result shows that the stereochemical outcome of the reaction is dictated by the chiral ketone **1** rather than the catalyst, as might be expected when considering the unique bent conformation of the cyclobutanone ring at the bicyclic core. This prompted us to evaluate simple pyrrolidine as a catalyst; pyrrolidine on its own did not result in any conversion but when one equivalent of acetic acid was added we obtained the product at a high conversion rate (Table 1, entry 5, 6).

In order to prove that the reaction was indeed operating through the postulated enamine intermediate, and did not simply involve the enol tautomer of ketone **1**, we performed the reaction with triethylamine as catalyst, with and without acetic acid; however no reaction was observed in any of these cases (Table 1, entry 7, 8), thus supporting the need for HOMO raising catalysis of the reaction. Aromatic aldehydes, i.e. benzaldehyde as the electrophile, did not result in any conversion in DMSO (Table 1, entry 9, 10). However, benzaldehyde and other liquid aldehydes, (e.g. 4-Methyl and 4-Fluoro benzaldehyde) gave the corresponding aldol product under neat reaction conditions (Table 1, entry 11) as detected by LC-MS. Unfortunately, purification via chromatography for all analogs except the benzaldehyde product **3** proved difficult since the β -lactam ring is prone to hydrolysis during elongated exposure to silica gel. However, aromatic aldehydes, i.e. 4-Nitro, 4-Methyl, 4-Methoxy, 4-Fluoro benzaldehyde and propionaldehyde, gave product upon changing solvent from DMSO to DMF, utilizing Pyrrolidine/AcOH as a catalyst. Again purification proved difficult; crude NMR yield for the reaction of these electrophiles with carbapenem ketone **1** were in the range 25-70 % as determined by crude NMR (Table 1, entries 12-19).

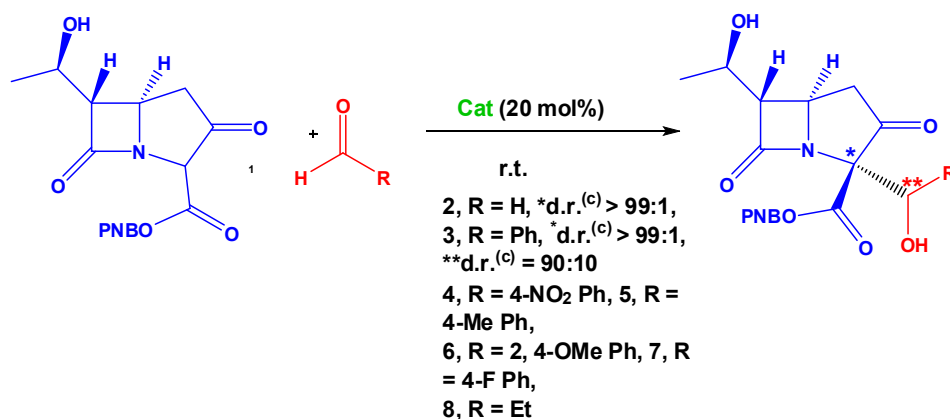


Table 1: Aldol reaction of carbapenam ketone intermediate **1** with aldehyde via enamine activation

| Entry | R | Catalyst/additive | Time [h] | Solvent | Yield (%) ^[b] |
|-------|--------------------------|------------------------|----------|-------------------|--------------------------|
| 1 | R = H | L-Proline | 24 | DMSO | 73 |
| 2 | R = H | L-Proline/AcOH | 24 | DMSO | 74 |
| 3 | R = H | L-Proline/AcOH | 8 | Neat | 76 |
| 4 | R = H | D-Proline | 24 | DMSO | 70 |
| 5 | R = H | Pyrrolidine | 24 | DMSO | NR |
| 6 | R = H | Pyrrolidine/AcOH | 2 | DMSO | 60 |
| 7 | R = H | NEt ₃ | 24 | DMSO | NR |
| 8 | R = H | NEt ₃ /AcOH | 24 | DMSO | NR |
| 9 | R = Ph | L-Proline | 24 | DMSO | NR |
| 10 | R = Ph | L-Proline/AcOH | 24 | DMSO | NR |
| 11 | R = Ph | L-Proline/AcOH | 6 | Neat ^a | 60 |
| 12 | R = Ph | L-Proline/AcOH | 24 | DMF | 25 ^d |
| 13 | R = Ph | Pyrrolidine/AcOH | 24 | DMF | 55 ^d |
| 14 | R = 4-NO ₂ Ph | Pyrrolidine/AcOH | 24 | DMF | 54 ^d |
| 15 | R = 4-Me Ph | Pyrrolidine/AcOH | 24 | DMF | 29 ^d |
| 16 | R = 4-OMe Ph | Pyrrolidine/AcOH | 24 | DMF | 51 ^d |
| 17 | R = 2,4-OMe Ph | Pyrrolidine/AcOH | 24 | DMF | 26 ^d |
| 18 | R = 4-F Ph | Pyrrolidine/AcOH | 24 | DMF | 46 ^d |
| 19 | R = Et | Pyrrolidine/AcOH | 48 | | 70 ^d |

^[a]Reactions were performed at excess amount of aldehyde to be as a solvent (see Supporting Information).

^[b]Isolated yields. ^[c]Diastereomeric ratio determined by ¹H NMR. ^[d]Observed yields from NMR of crude reaction mixture.

The formation of the new C-C bond in product **2** was confirmed by observing the shift of C₈ from 64.0 ppm (1) to 131.6 ppm (2) in ¹³C NMR and disappearance of H₈ as a singlet at 4.76 ppm (1) in H-NMR, **Figure 2**. In addition, protons at C₁₇ showed an HMBC correlation with C₈. The 2D NMR investigation proved the excellent stereoselectivity (d.r. > 99:1) seen in the crude LC-MS trace and 1D spectra, and through a correlation between H₁₇ and H₄ in the NOESY spectra we could establish the expected *exo*-configuration of the newly attached group in **2**. Compound **3** showed similar HMBC correlations and excellent diastereoselectivity as observed with **2** for the formation of the C-C bond at C₈. The newly formed chiral centre C₁₇ in compound **3** was determined to be created with a diastereomeric ratio of 90:10.

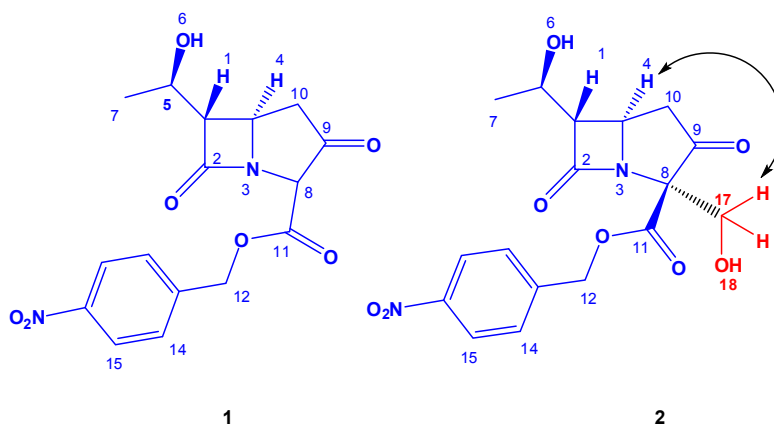
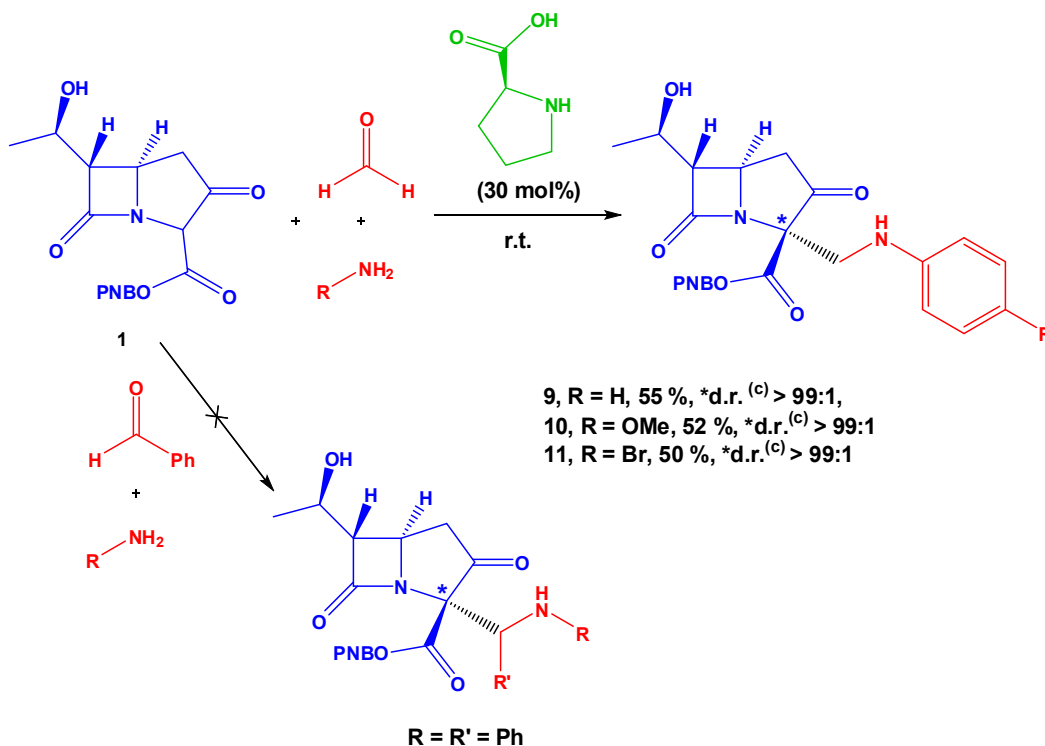


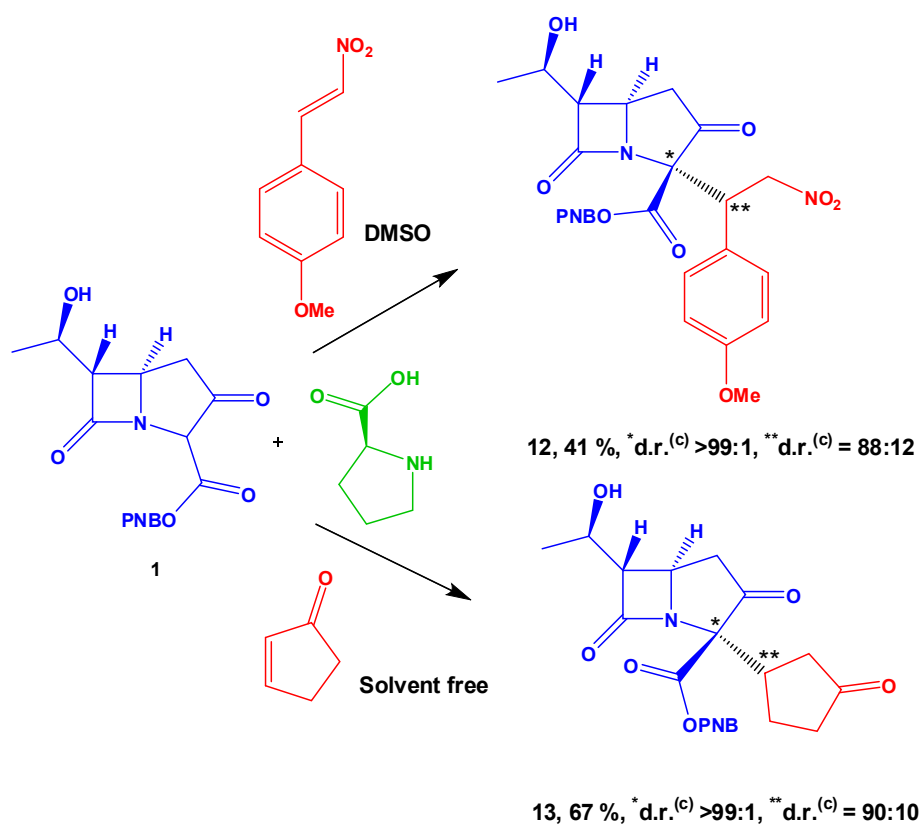
Figure 2: Aldol Product **2**, resulting from L-Proline catalyzed transformation of “carbapenam ketone” **1** and Formaldehyde

Given the high potential for using organocatalysis for accessing hitherto unexplored derivatives of carbapenam and carbapenem β -lactams, we decided to explore other organocatalyzed processes, i.e. Mannich and Michael reactions. First, we decided to perform the direct asymmetric three-component Mannich reaction of carbapenam intermediate **1** with different amines and aldehydes in DMSO. In the presence of 30% L-Proline, aldehydes and amines were reacted with **1** to give products **9**, **10** and **11** in moderate yields (50% to 55%) respectively. These yields are typical of the one pot Mannich reaction and are attributed to the formation of the competitive aldol reaction side products as noticed by LC-MS. Various aromatic aldehydes were tested as electrophiles, but, similarly to the aldol reaction described above, only formaldehyde resulted in the formation of the Mannich adducts. A complete NMR assignment of Mannich product **9** proved the *exo*-product was formed with complete diastereoselectivity, in analogy to the aldol product **2** above. In compound **9**, the absolute configuration at C₈ was confirmed by NOE correlation (See SI).



Scheme 2: Mannich Reactions on Carbapenam intermediate **1**

Next, we explored the organocatalyzed Michael reaction to carbapenam intermediate **1**. The most commonly studied Michael acceptors with enamine catalyzed reactions are nitrostyrenes^{28, 36} and enones;³⁷ hence it was decided to test these substrates in this first report. From the optimized conditions reported above, we initiated the study by examining the addition of the carbapenam intermediate **1** to *trans*-4-methoxy- β -nitrostyrene in DMSO catalyzed by L-Proline. The reaction offered the product **12** in modest 41% yield in 24 hours. The modest yield was due to low catalytic turnover, as confirmed through LC-MS analysis of the crude mixture, where we noticed a peak that corresponded to the Michael product still bound to the catalyst. To release the product, the adduct had to be stirred with water and monitored by LC-MS until only a minor amount of trapped product could be detected. Similarly, Michael reaction of carbapenam intermediate **1** with neat cyclopentenone using L-Proline as catalyst produced compound **7** in 67% yield.



Scheme 3. Michael Reaction on Carbapenam intermediate **1**

The observed HMBC correlation between H₁₇ and C₈ in both compounds (**12** and **13**) proved the formation of the new C-C bond at this position. From the ¹H NMR shifts of H₁₇ in compound **12** and **13**, the diastereomeric ratio was established to be 88:12 and 90:10 respectively. The configuration at C₈ for **12** was also established by NOE correlation as for the aldol and Mannich reactions above.

Conclusions

In summary, the mild reaction conditions that characterize enamine-based organocatalysis have been shown to offer a new route to chiral β-lactam derivatives. The reaction scope has so far been shown to include aldol, Mannich and Michael reactions. High distereoselectivity was observed in all of the reactions, as would be expected considering the inherent chirality of the starting carbapenam intermediate. This methodology has the potential to offer, a widely sought after, new synthetic route to novel and potentially medically useful β-lactam antibiotics. The full substrate scope for the Mannich and Michael reactions reported here are ongoing in our laboratories.

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Supporting information

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CHAPTER 3

Organocatalyzed Synthesis of Monobactam and Carbapenem β -Lactam cores through L-Proline catalyzed asymmetric Michael reactions

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Abstract

Herein, we report the development of mild, organocatalyzed routes to novel β -lactam carbapenam derivatives through Michael type C–C bond forming reactions. The same methodology, followed by a retro-Dieckmann reaction, provides a pathway to novel and highly functionalized monobactam derivatives – another class of valuable β -lactam antibiotics.

Introduction

The efficient generation of a new C–C bonds may be seen as the essence of synthetic organic chemistry, as it allows the preparation of valuable natural and unnatural compounds.^{1, 2} The Michael addition reaction is well known as one of the most widely used C–C bond-forming reactions in organic synthesis.^{1, 2} Similarly, an increased interest in optically active molecules has promoted a considerable interest in the development of more efficient catalytic stereoselective methods.^{3, 4} Asymmetric organocatalysis has emerged as a new powerful methodology for the catalytic production of enantiomerically pure organic compounds, and is subsequently one of the most rapidly growing research areas in synthetic organic chemistry.^{3, 5, 6} Organocatalysis through enamine activation,⁷ is essentially the use of primary and secondary amines to facilitate electrophilic substitution reactions; typically, at the

α -position of carbonyl compounds via HOMO-raising strategies.⁸⁻¹² We recently communicated our introductory result on the first amino catalyzed stereospecific C-C bond forming reaction on a β -lactam core through Aldol, Mannich¹³ and Michael-type reactions.¹⁴ β -Lactams of the penicillin class (**Figure 1**) were among the first antimicrobial agents for the treatment of infectious diseases.^{15, 16} Various other β -lactam containing drugs has since been developed as powerful antibiotics, e.g. monobactams like Aztreonam and carbapenems like Imipenem. The carbapenem subgroup possesses the broadest spectrum of activity and the greatest potency against Gram-positive and negative bacteria.

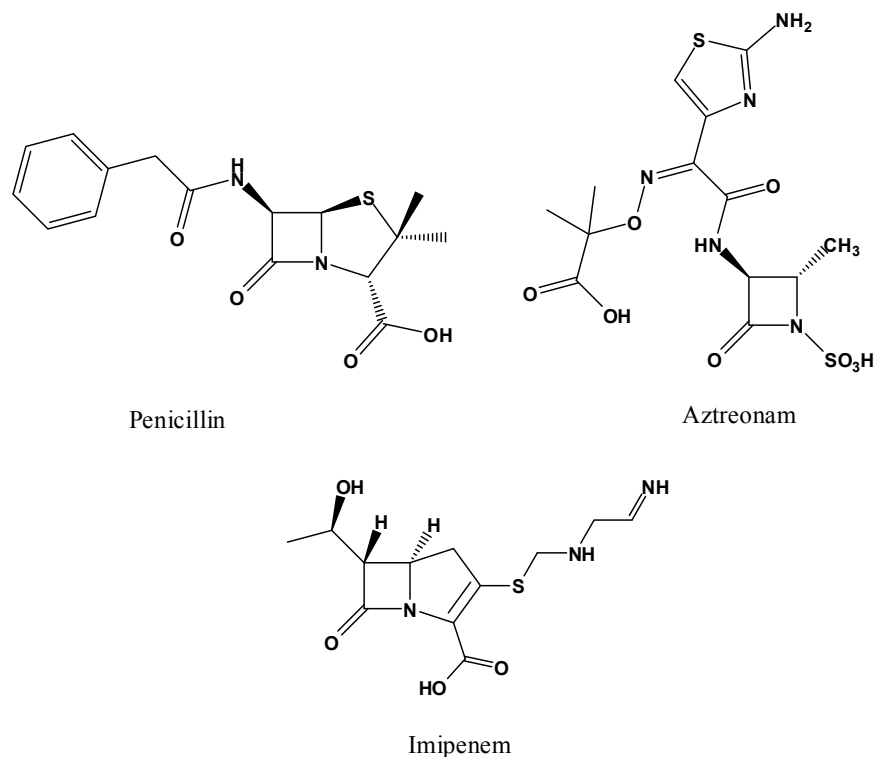


Figure 1: Representative antimicrobial agents bearing a β -Lactam core.

As a result, this class is often used as antibiotics of last resort for critically ill patients.^{15, 17-19} The recent emergence of multidrug-resistance (MDR) pathogens have seriously constrained the efficiency of these agents.^{19, 20} Hence, the global threat of antimicrobial drug resistance has prompted the search and development of new antibacterial agents based on this pharmaceutically relevant skeleton. Herein we report an expansion of the scope of the mild organocatalytic asymmetric Michael addition transformation on the carbapenem core **1** we previously reported. L-Proline was used as catalyst with different electrophilic substrates, such as chalcones, which are precursors of flavonoids and isoflavonoids that possess a wide variety of biological activities.²¹ Similarly, cyclic enones, known to be part of a variety of bioactive compounds, was also employed.²²⁻²⁵ Most important, we, for the first time, demonstrate a new

transformation of the optically active Michael product into a monocyclic β -lactam structure. Such monobactams represent another important subclass of antibacterial agents.

Results and Discussion

Based on our initial report, for the reaction between carbapenem core **1** and trans-4-methoxy- β -nitrostyrene,¹⁴ we examined the substrate scope of the asymmetric Michael addition with other electrophilic olefins, (Table1). As previously reported, trans-4-methoxy- β -nitrostyrene proceeded smoothly to afford product **3a** in modest yield (41%) and good dr (88:12) (Table 1, entry 1). For nitrostyrene, yielding **3b**, relatively poor dr (60:40) was obtained although yield (42%) were similar as compared with **3a** (Table 1, entries 1 and 2, respectively). It was found that changing to a more electron-withdrawing substituent on the aromatic ring did not affect the selectivity as product **3c** was produced in similar yield (45%) and dr (87:13) as compared with **3a**. To further explore the substrate scope, benchmark organonitriles were examined. Unfortunately only trace amounts were observed via LC-MS analysis of the crude reaction mixture (Table 1, entries 4 and 5 respectively).

Table 1. Substrate scope for the catalytic Michael addition with electron deficient olefin.

| Entry | R ₁ | R ₂ | Time [h] | Product | Yield [%] ^[b] | dr ^[c] |
|-------|-------------------|------------------------------------|----------|-----------|--------------------------|-------------------|
| 1 | NO ₂ | 4-MeOC ₆ H ₄ | 24 | 3a | 41 | 88:12 |
| 2 | NO ₂ | C ₆ H ₅ | 20 | 3b | 42 | 60:40 |
| 3 | NO ₂ | 4-ClC ₆ H ₄ | 17 | 3c | 46 | 87:13 |
| 4 | CN | H | 72 | trace | | |
| 5 | (CN) ₂ | H | 72 | trace | | |

[a] The reaction was carried out with carbapenem **1** (0.574 mmol) and **2** (2 eq.) in DMSO (0.5 mL). [b] Yield of isolated product. [c] Diastereomeric ratio determined by ¹H NMR.

Having explored electron deficient olefins, we next evaluated the asymmetric Michael additions of various α,β -unsaturated ketones and β,γ -unsaturated α -ketoesters on the carbapenam intermediate **1** by using 20 mol% of L-proline as a catalyst, Table 2. The reactions were complete within 15-35h and gave products in moderate yields (55- 67%) and good dr (88:12–92:8). Reactions were general for both 5 and 6- membered α,β -unsaturated cyclic enones with good yields of products **5a** and **5b** (67 and 63%) and dr (90:10) (Table 2, entries 1 and 2 respectively). Olefins substituted at the α or β positions, did not give any conversion after 40h (Table 2, entries 3 and 4). Methylvinylketone and vinyl ester also proved to be inefficient Michael acceptors (Table 2, entries 5 and 6) for the carbapenam donor **1**. Acyclic α,β -unsaturated ketone furnished product **5c** in good yields (63%) and dr (91:9) (Table 2, entry 7), while the α,β -unsaturated ester analogue was non-reactive (Table 2, entry 8). β,γ -Unsaturated α -ketoesters bearing either electron-withdrawing or electron-donating substituents, worked well and give the desired products **5d-5f** in moderate yields (55-60%) and good dr (88:12-92:8).

Table 2. Substrate scope for the catalytic Michael addition reaction with α,β -unsaturated ketones and various β,γ -unsaturated α -ketoesters.

| Entry | Substrate | Time [h] | Product | Yield [%] ^[b] | dr ^[c] |
|-------|-----------|----------|-----------|--------------------------|-------------------|
| 1 | | 24 | 5a | 67 | 90:10 |
| 2 | | 24 | 5b | 63 | 90:10 |
| 3 | | 40 | NR | | |
| 4 | | 40 | NR | | |
| 5 | | 40 | NR | | |
| 6 | | 40 | NR | | |
| 7 | | 15 | 5c | 63 | 91:9 |
| 8 | | 55 | NR | | |
| 9 | | 31 | 5d | 60 | 90:10 |
| 10 | | 24 | 5e | 62 | 88:12 |
| 11 | | 35 | 5f | 55 | 92:8 |

[a] The reaction was carried out with carbapenem **1** (0.574 mmol) and **4** (2 eq) in DMSO (0.5 mL). [b] Yield of isolated product. [c] Diastereomeric ratio determined by ¹H NMR

Formation of the new C-C bond in product **3a** was confirmed by observing the shift of C₈ from 64.0 ppm for **1** to 76.4 ppm for **3a** in ¹³C NMR spectrum and disappearance of H₈ as a singlet at 4.76 ppm for **1** in ¹H NMR spectrum (**Figure 2**). In addition H₁₇ showed HMBC correlation with C₈. From elucidation of the 2D spectra we established a NOESY correlation between H₄ and H₁₉ which confirmed the *exo* configuration of the newly attached group in **3a**. The newly formed chiral centers at C₈ and C₁₇ in compound **3a** was determined to be created with a diastereomeric ratio of 88:12.

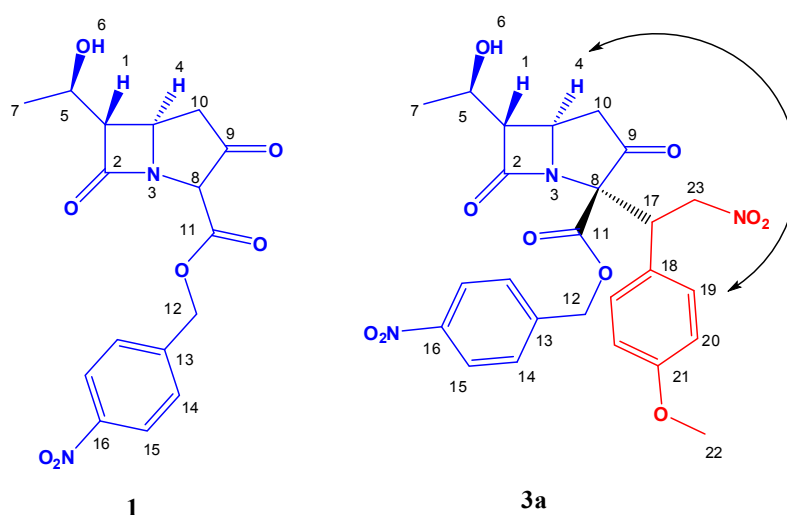
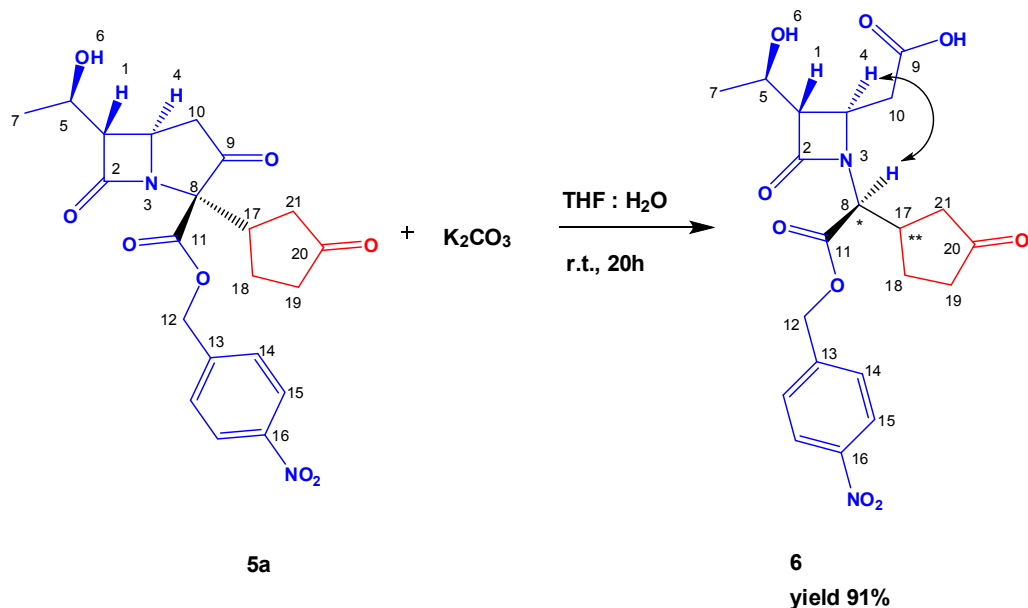


Figure 2: Numbering used for the NMR assignment of carbapenem intermediate **1** and Michael product **3a**

Next we found that treatment of the Michael products, e.g. **5a**, with potassium carbonate in aqueous THF (**Scheme 1**) led to ring-opening of the 5-membered ketone ring through a retro-Dieckmann condensation.²⁶ The monocyclic β -lactam thereby obtained, i.e. **6**, represent another important class of antibacterial agents – a monobactam. From the ¹³C NMR spectrum we observed the shift of C₉ at 208.0 ppm for **5a** to 173.3 ppm for **6** (indicative of an acid group) and C₈ at 76.6 ppm for **5a** to 59.9 ppm for **6**. In addition C₉ showed the same HMBC correlation with H₁₀ protons as in **5a**. In ¹H NMR spectrum, a new H₈ signal appeared at 4.09 ppm for **6** which showed HMBC correlation with C₁₇ and C₁₁. From the NOESY spectra, we observed a correlation between H₈ and H₄ thus confirming the configuration of the newly attached H₈ proton.



Scheme 1: Synthesis of product **6**

There are several reported methods for the synthesis of monocyclic β -lactams including named reactions as the classic Staudinger,²⁷ Reformatsky²⁸ and Kinugasa.²⁹ More recently, organocatalysts have been employed in an effort to make the Staudinger reaction more efficient.³⁰ However, to the best of our knowledge this is the first report where a sequential use of an organocatalytic Michael reaction followed by a retro-Dieckmann reaction transforms a bicyclic- β -lactam, i.e. carbapenem, into a monocyclic- β -lactam, i.e. monobactam, with the addition of two chiral centers.

Conclusions

In summary, we have demonstrated the possibility to synthesize novel β -lactam derivatives by utilizing the organocatalysed Michael addition reaction on the carbapenem intermediate **1** with various electrophilic olefins i.e. α,β -unsaturated ketones and β,γ -unsaturated α -ketoesters. Good yields and some excellent diastereoselectivities were obtained with L-proline as the organocatalyst. The obtained Michael products could be smoothly interconverted to monobactams through a retro-Dieckmann reaction, thereby leading to another highly valued class of β -lactam antibiotics.

Experimental

General methods

Reagents and solvents were purchased from Sigma Aldrich and Merck. All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instruments at room temperature. Chemical shifts are expressed in ppm downfield from TMS as an internal standard, and coupling constants are reported in Hz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using silica gel (60–200 mesh unless otherwise stated). All solvents were dried using standard procedures. Optical rotations were recorded on a Perkin-Elmer Polarimeter (Model 341). High-resolution mass spectrometric data were obtained using a Bruker micrO TOF-Q II instrument operating at ambient temperatures and a sample concentration of approximately 1 ppm.

Representative procedure for the Michael addition reaction of olefins, α,β -unsaturated ketones and β,γ -unsaturated α -keto-ester with carbapenem:

To a stirred solution of compound **1** (0.574 mmol) and catalyst (0.115 mmol) in DMSO (0.5 mL) at room temperature, was added Michael acceptor (2.0 eq.). The mixture was stirred at ambient temperature for 24 h while being monitored by TLC. The reaction mixture was then quenched by adding water (5 mL) and the aqueous layer was extracted three times with DCM (30 mL). The combined organic layers were dried with MgSO_4 , which was subsequently removed by filtration. The concentrated extract was subjected to silica gel for purification to afford the desired product.

Representative procedure for the synthesis of product **6**

To a stirred solution of compound **5a** (500 mg) at room temperature was added K_2CO_3 (20 mg) in 2:1 THF and H_2O respectively. The mixture was stirred at ambient temperature for 12h while being monitored by TLC. The reaction mixture was then quenched by adding 30 % acetic acid and the aqueous layer was extracted five times with ethyl acetate (30 mL). The combined organic layers were dried with MgSO_4 , which was subsequently removed by filtration. The concentrated extract was dried vacuum to afford the desired product.

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (**3a**)

The crude product was purified by column chromatography (ethylacetate/hexane, 50:50; $R_f = 0.2$) to afford the product (124 mg, 41%) as a semi solid. $[\alpha]_{20}^D = +156.7$ ($c = 0.1$, CHCl_3) ^1H NMR (400 MHz,

CDCl₃): δ 8.24 (d, J = 8.60 Hz, 2H), 7.48 (d, J = 8.60 Hz, 2H), 7.21 (d, J = 8.68 Hz, 2H), 6.82 (d, J = 8.72 Hz, 2H), 5.32 (m, 2H), 5.00 (dd, J = 13.17, 11.17 Hz, 2H), 4.36 (dd, J = 11.11, 4.10 Hz, 1H), 4.10 (m, 1H), 3.56 (m, 1H), 3.12 (dd, J = 5.20, 2.56 Hz, 1H), 2.43 (dd, J = 8.80, 8.72 Hz, 1H), 2.27 (dd, J = 6.88, 6.96 Hz, 1H), 1.29 (d, J = 6.28 Hz, 3H) ppm. ¹³C NMR (100 MHz CDCl₃): δ 207.3, 171.5, 164.9, 160.9, 141.7, 131.7, 129.1, 124.1, 114.5, 94.5, 74.3, 67.3, 67.1, 55.4, 55.0, 51.1, 44.1, 40.5, 21.2 ppm. HRMS (ESI+) m/z calcd. for C₂₅H₂₅N₃O₁₀: 527.1612; found [M+H] 528.3160

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*R*)-2-nitro-1-phenylethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3b)

The crude product was purified by column chromatography (ethylacetate /hexane, 50:50; R_f = 0.2) to afford the product (120 mg, 42%) as a semi solid [α]₂₀^D = +90.6 (c = 0.1, CHCl₃) ¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, J = 8.28 Hz, 2H), 7.41 (d, J = 8.08 Hz, 2H), 7.20 (m, 5H), 5.10 (m, 3H), 4.91 (dd, J = 13.91, 6.22 Hz, 2H), 4.35 (m, 1H), 4.03 (m, 1H), 3.35 (m, 1H), 2.99 (m, 1H), 2.34 (dd, J = 9.12, 8.60, 1H), 2.17 (dd, J = 7.63, 6.78 Hz, 1H), 1.21 (d, J = 5.96 Hz, 3H) ppm. ¹³C NMR (100 MHz CDCl₃): δ 207.1, 172.0, 165.0, 141.7, 135.4, 132.7, 129.9, 129.0, 128.9, 128.8, 124.0, 76.2, 74.8, 67.6, 67.4, 64.4, 50.9, 44.2, 40.2, 21.9 ppm. HRMS (ESI+) m/z calcd. for C₂₄H₂₃N₃O₉: 497.1410; found [M+H] 498.1483

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*R*)-1-(4-chlorophenyl)-2-nitroethyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3c)

The crude product was purified by column chromatography (ethylacetate /hexane, 50:50; R_f = 0.2) to afford the product (140 mg, 46%) as a semi solid [α]₂₀^D = +101.0 (c = 0.1, CHCl₃) ¹H NMR (400 MHz, CDCl₃): δ 8.18 (d, J = 8.18 Hz, 2H), 7.41 (d, J = 8.64 Hz, 2H), 7.21 (m, 4H), 5.25 (m, 2H), 4.84 (dd, J = 13.50, 11.19 Hz, 2H), 4.33 (dd, J = 11.11, 3.98 Hz, 1H), 4.20 (m, 1H), 3.41 (m, 1H), 3.06 (dd, J = 4.78, 2.50, 1H), 2.38 (dd, J = 8.92, 8.96 Hz, 1H), 2.23 (dd, J = 6.84, 6.88 Hz, 1H), 1.21 (d, J = 6.32 Hz, 3H) ppm. ¹³C NMR (100 MHz CDCl₃): δ 206.2, 171.6, 164.3, 140.6, 135.1, 131.3, 131.1, 129.2, 129.1, 124.1, 76.0, 74.2, 67.7, 67.5, 64.3, 50.6, 43.8, 40.2, 21.7 ppm. HRMS (ESI+) m/z calcd. for C₂₄H₂₂N₃O₉: 531.1023; found [M+H] 532.1073

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxocyclopentyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5a)

The crude product was purified by column chromatography (ethylacetate /hexane, 50:50; R_f = 0.2) to afford the product (165 mg, 67%) as a semi solid. [α]₂₀^D = +215.0 (c = 0.1, CHCl₃) ¹H NMR (400 MHz, CDCl₃): δ 8.22 (d, J = 7.16 Hz, 2H), 7.45 (d, J = 8.56 Hz, 2H), 5.27 (s, 2H), 4.25 (s, 1H), 4.03 (s, 1H), 3.29 (t, 1H), 3.17 (d, 1H), 2.97- 2.95 (d, J = 11.05 Hz, 1H), 2.55- 2.39 (dd, J = 17.91, 8.58 Hz, 2H), 2.19

(d, J = 9.49 Hz, 2H), 2.04 (d, J = 7.08 Hz, 1H), 1.80 (d, J = 19.61 Hz, 1H), 1.34 (d, J = 4.80 Hz, 3H) ppm. ^{13}C NMR (100 MHz CDCl_3): δ 215.3, 208.0, 164.9, 161.0, 140.8, 128.7, 124.5, 76.6, 66.5, 66.2, 64.9, 50.2, 42.1, 40.9, 38.4, 38.0, 23.6, 21.9 ppm. HRMS (ESI-) m/z calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_8$: 429.1292; found [M-H] 429.1440

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxocyclohexyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5b)

The crude product was purified by column chromatography (ethylacetate /hexane, 50:50; R_f = 0.2) to afford the product (161 mg, 63%) as a semi solid. $[\alpha]_{20}^D = +43.2$ (c = 0.1, CHCl_3) ^1H NMR (400 MHz, CDCl_3): δ 8.22 (d, J = 8.64 Hz, 2H), 7.45 (d, J = 8.46 Hz, 2H), 5.24 (d, J = 11.34 Hz, 2H), 4.33 (m, 1H), 3.96 (m, 1H), 3.27 (m, 1H), 2.89 (m, 1H), 2.76 (m, 2H), 2.68 (m, 2H), 2.40 (m, 2H), 2.25 (m, 2H), 2.04 (m, 2H), 1.29 (d, J = 5.10 Hz, 3H) ppm. ^{13}C NMR (100 MHz CDCl_3): δ 209.2, 208.6, 170.8, 164.1, 147.9, 141.8, 128.4, 124.0, 67.6, 67.0, 64.6, 50.7, 42.9, 41.4, 41.0, 40.9, 25.7, 24.3, 21.7 ppm. HRMS (ESI+) m/z calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_8$: 444.1292; found [M+Na] 467.144

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*S*)-3-oxo-1-phenylbutyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5c)

The crude product was purified by column chromatography (ethylacetate /hexane, 60:40; R_f = 0.2) to afford the product (179 mg, 63%) as a semi solid $[\alpha]_{20}^D = +80$ (c = 0.1, CHCl_3) ^1H NMR (400 MHz, CDCl_3): δ 8.23 (d, J = 8.64 Hz, 2H), 7.48 (d, J = 8.64 Hz, 2H), 7.22 (m, 5H), 5.32 (dd, J = 12.96, 12.93 Hz, 2H), 4.19 (m, 1H), 4.14 (dd, J = 5.44, 5.48 Hz, 2H), 3.39 (m, 1H), 3.18 (m, 2H), 3.12 (dd, J = 2.48, 2.52 Hz, 1H), 2.38 (dd, J = 8.84, 8.80 Hz, 1H), 2.17 (dd, J = 6.88, 6.88 Hz, 1H), 2.05 (s, 3H), 1.30 (d, J = 6.32 Hz, 3H) ppm. ^{13}C NMR (100 MHz CDCl_3): δ 208.3, 205.6, 171.4, 165.1, 148.0, 141.4, 136.8, 129.9, 128.8, 128.6, 127.8, 123.9, 76.8, 67.2, 67.0, 64.8, 50.9, 45.4, 41.7, 40.5, 30.4, 21.6 ppm. HRMS (ESI+) m/z calcd. For $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_8$: 494.1712; found [M+H] 495.1797

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-4-methoxy-3,4-dioxo-1-phenylbutyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5d)

The crude product was purified by column chromatography (ethylacetate /hexane, 60:40; R_f = 0.2) to afford the product (189 mg, 60%) as a semi solid $[\alpha]_{20}^D = +40.1$ (c = 0.1, CHCl_3) ^1H NMR (400 MHz, CDCl_3): δ 8.23 (d, J = 8.36 Hz, 2H), 7.48 (d, J = 8.40 Hz, 2H), 7.23 (m, 5H), 5.17 (dd, J = 12.88, 12.88 Hz, 2H), 4.29 (m, 1H), 4.20 (dd, J = 4.01, 4.01 Hz, 1H), 3.78 (s, 3H), 3.61 (m, 2H), 3.40 (m, 1H), 3.12 (dd, J = 2.51, 2.50 Hz, 1H), 2.42 (dd, J = 8.79, 8.76 Hz, 1H), 2.21 (dd, J = 6.82, 6.79 Hz, 1H), 1.30 (d, J = 6.12 Hz, 3H) ppm. ^{13}C NMR (100 MHz CDCl_3): δ 208.4, 191.5, 171.2, 165.6, 161.0, 148.4, 141.7, 136.4,

130.0, 128.9, 128.6, 128.0, 123.9, 76.4, 67.4, 67.1, 64.7, 53.0, 50.7, 41.5, 40.6, 21.6 ppm. HRMS (ESI+) m/z calcd. for $C_{27}H_{26}N_2O_{10}$: 538.5011; found $[M+H]$ 539.1694

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*S*)-1-(4-fluorophenyl)-4-methoxy-3,4-dioxobutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5e)

The crude product was purified by column chromatography (ethylacetate /hexane, 60:40; R_f = 0.2) to afford the product (198 mg, 62%) as a semi solid $[\alpha]_{20}^D = +50.2$ (c = 0.1, $CHCl_3$) 1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.60 Hz, 2H), 7.40 (d, J = 8.60 Hz, 2H), 7.21 (d, J = 5.68 Hz, 2H), 6.88 (d, J = 8.50 Hz, 2H), 5.09 (dd, J = 12.88, 12.88 Hz, 2H), 4.21 (m, 1H), 4.13 (dd, J = 5.04, 5.04 Hz, 1H), 3.71 (s, 3H), 3.50 (m, 2H), 3.31 (m, 1H), 3.06 (dd, J = 2.36, 2.34 Hz, 1H), 2.35 (dd, J = 8.88, 8.79 Hz, 1H), 2.18 (dd, J = 6.86, 6.69 Hz, 1H), 1.22 (d, J = 6.28 Hz, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ 208.4, 191.3, 172.2, 165.2, 163.5, 161.0, 148.0, 141.2, 132.0, 131.6, 128.9, 123.9, 115.4, 76.3, 67.4, 67.1, 64.5, 53.0, 50.7, 41.7, 40.6, 40.5, 21.6 ppm. HRMS (ESI+) m/z calcd. for $C_{27}H_{25}N_2O_{10}$: 556.1345; found $[M+H]$ 557.1023

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*S*)-1-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-3,4-dioxobutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5f)

The crude product was purified by column chromatography (ethylacetate /hexane, 60:40; R_f = 0.2) to afford the product (184 mg, 55%) as a semi solid $[\alpha]_{20}^D = +97.3$ (c = 0.1, $CHCl_3$) 1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.52 Hz, 2H), 7.40 (d, J = 8.56 Hz, 2H), 6.64 (m, 3H), 5.84 (d, J = 7.08, 2H), 5.10 (dd, J = 12.88, 12.84 Hz, 2H), 4.22 (m, 1H), 4.05 (dd, J = 4.64, 4.32 Hz, 1H), 3.71 (s, 3H), 3.46 (m, 2H), 3.05 (dd, J = 2.24, 2.36 Hz, 1H), 2.35 (dd, J = 8.88, 8.88 Hz, 1H), 2.16 (dd, J = 6.88, 6.88 Hz), 1.22 (d, J = 6.28 Hz, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ 208.4, 191.2, 171.5, 165.2, 161.3, 148.0, 147.2, 141.2, 129.8, 128.9, 123.9, 123.3, 110.3, 108.3, 101.2, 76.4, 67.1, 64.8, 53.0, 50.9, 41.9, 40.9, 40.6, 21.5 ppm. HRMS (ESI+) m/z calcd. For $C_{28}H_{26}N_2O_{12}$: 582.1542; found $[M+H]$ 583.1534

2-((2*R*,3*S*)-3-(1-Hydroxyethyl)-1-(2-(4-nitrobenzyloxy)-2-oxo-1-(3-oxocyclopentyl)ethyl)-4-oxoazetidin-2-yl)acetic acid (6)

Product was afforded as a semi solid, yield (474 mg, 91%), $[\alpha]_{20}^D = -17.4$ (c = 0.1, $CHCl_3$) 1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.60 Hz, 2H), 7.48 (d, J = 8.32 Hz, 2H), 5.16 (d, J = 5.24 Hz, 2H), 4.09 (m, 1H), 3.98 (m, 1H), 3.88 (m, 1H), 2.87 (m, 1H), 2.81 (m, 1H), 2.76 (m, 2H), 2.58 (m, 2H), 2.17 (m, 2H), 1.99 (m, 2H), 1.21 (d, J = 6.36 Hz, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ 217.1, 173.3, 168.5, 167.4, 147.9, 141.7, 128.9, 123.8, 66.1, 65.8, 63.0, 59.9, 53.5, 52.1, 42.7, 38.3, 37.9, 37.2, 36.6, 27.2, 21.0 ppm. HRMS (ESI-) m/z calcd. for $C_{21}H_{24}N_2O_9$: 448.1510; found $[M-H]$ 447.012

Acknowledgements

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Supporting Information

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CHAPTER 4

Summary

In summary, the mild reaction conditions that characterize enamine-based organocatalysis have been shown to offer new routes to novel chiral β -lactam derivatives. The first organocatalysed C-C bond forming reactions have been performed on the carbapenem intermediate **1**, was the Aldol reaction, with various aldehydes to afford the corresponding products in good yields (up to 76%) and excellent diastereoselectivities (up to 99:1 ratios). Next, the Mannich reaction was evaluated with different amines and aldehydes. The products were obtained with modest chemical efficiency (up to 55%) and excellent diastereoselectivities (up to 99:1 ratios) as with the Aldol reaction. The reactivity of the carbapenem intermediate **1** was also evaluated in the Michael addition reaction with electrophilic olefins such as α,β -unsaturated ketones and β,γ -unsaturated α -ketoesters. Good yields (up to 67%) and some excellent diastereoselectivities (up to 92:8 ratios) were obtained with L-proline as the organocatalyst. We have also demonstrated the possibility to effectively interconvert the Michael products to monobactams through a retro-Dieckmann reaction under basic conditions, thereby leading to another highly valued class of β -lactam antibiotics.

SUPPORTING INFORMATION FOR CHAPTER 2

UNIVERSITY OF KWAZULU-NATAL

**ORGANOCATALYZED SYNTHESIS OF
CARBAPENEM β -LACTAM CORES AND
MONOBACTAM**

2014

SIBUSISO KHANYASE

Contents

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NMR

The observed NOE interaction between H₄ and H₁₈ in Mannich compound **9** that confirms the absolute configuration at C₈ is presented in Figure 1. This long range interaction (black arrow) supports the presence of similar configuration at C₈ like Aldol reaction (See Figure 1).

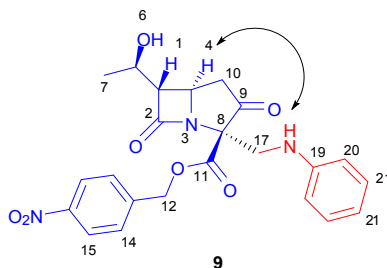


Figure 1: Long range interaction in compound **9**

Experimental

Reagents and solvents were purchased from Sigma Aldrich and Fluka Chemicals. All NMR spectra were recorded on Bruker AVANCE III 400 MHz instrument. The chemical shifts are expressed in ppm downfield from TMS as the internal standard and the coupling constants are reported in Hertz. Thin layer chromatography was performed using Merck Kieselgel 60 F254. Compounds were purified by column chromatography packed with 60-200 mesh Silica gel and Shimadzu C18 column prep HPLC. Optical rotations were recorded on a Perkin-Elmer Polarimeter (Model 341). High resolution spectrometric data were obtained using Bruker maxis 4G instrument operating at ambient temperatures.

General Procedure for Aldol reaction

A mixture of compound **1** (1.0 eq) and aldehyde (10.0 eq) was stirred in the presence of catalyst (0.2 eq) and acetic acid (0.2 eq) at room temperature. Pyrrolidine, L-proline and D-proline were used in turns as catalysts in the reactions for all the substrates that were tested. The reaction progress was monitored using TLC and LCMS, on completion the reactions were quenched using water and extracted with DCM (30 mL x 3). The extracts were dried with Mg₂SO₄, which was subsequently removed by filtration. The

solvent was removed under reduced pressure, and the crude product mixture was purified by column chromatography. The structure was confirmed using NMR and Mass.

(2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-(hydroxymethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (2)

The crude product was purified by column chromatography (ethylacetate/hexane, 70:30; $R_f = 0.3$) to afford the product (76%) as a colorless oil. $[\alpha]_{20}^D = -26.6$ ($c = 0.1$, CHCl_3) ^1H NMR (400 MHz, DMSO): δ 8.26 (d, $J = 8.56$ Hz, 2H), 7.69 (d, $J = 8.56$ Hz, 2H), 5.86 (s, 1H), 5.37 (s, 1H), 5.32 (dd, $J = 9.37$ Hz, 2H), 4.48 – 4.49 (m, 1H), 4.17 (p, 1H), 2.95 – 3.04 (m, 2H), 2.58 (q, $J = 16.87$, $J = 9.62$, 1H), 1.33 (d, $J = 6.28$ Hz, 3H); ^{13}C NMR (100 MHz DMSO): δ 171.9, 166.1, 161.9, 148.1, 143.8, 131.6, 128.3, 124.3, 114.1, 65.5, 63.5, 62.6, 52.9, 37.4, 21.6; HRMS (ESI-) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_8$: 377.0979; found [M-H] 377.1391

(2*S*,5*R*,6*S*)-4-nitrobenzyl 2-((*R*)-hydroxy(phenyl)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3)

The crude product was purified by column chromatography (ethylacetate /hexane, 70:30; $R_f = 0.2$) to afford the product (60%) as a semisolid. $[\alpha]_{20}^D = +20.0$ ($c = 0.1$, CHCl_3) ^1H NMR (600 MHz, DMSO): δ 8.25 (d, $J = 8.52$ Hz, 2H), 7.74 (d, $J = 8.52$ Hz, 2H), 7.69 (m, 2H), 7.53 (s, 1H), 7.42 (m, 3H), 5.41 (s, 2H), 4.35 (m, 1H), 3.96 (m, 1H), 3.02 (d, $J = 2.58$, 6.3 Hz, 1H), 2.61 (m, 2H), 1.13 (d, $J = 8.52$ Hz, 3H); ^{13}C NMR (150 MHz DMSO): δ 172.5, 167.2, 163.3, 147.2, 143.6, 136.4, 132.3, 130.3, 128.6, 128.6, 128.3, 122.6, 65.5, 63.9, 62.3, 53.5, 38.0, 22.3; HRMS (ESI-) m/z calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_8$: 453.1292; found [M-H] 453.1694

General Procedure for Mannich reaction

To a stirred solution of formaldehyde (2.0 eq, 36% aqueous solution) in DMSO (3 mL), substituted amine (2.0 eq) was added at ambient temperature. After 2 h, the compound **1** (1.0 eq) and catalyst (0.3 eq) were added and the reaction mixture was stirred for 20 h while being monitored using TLC. The reaction mixture was then quenched by addition of PBS buffer (1 mL), water (3 mL) and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with Mg_2SO_4 , which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure, and the crude product mixture was purified by column chromatography.

(2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((phenylamino)methyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (9)

The crude product was purified by column chromatography (ethylacetate/hexane, 80:20; R_f = 0.4) to afford the product (55%) as a semisolid. $[\alpha]_{20}^D = -30.0$ ($c = 0.1$, CHCl_3) ^1H NMR (400 MHz, CDCl_3): $\delta = 8.21$ (d, $J = 8.64$ Hz, 2 H), 7.70 (s, 1 H), 7.51 (d, $J = 8.60$ Hz, 2H), 7.45 (d, $J = 7.88$ Hz, 2 H), 7.30 (t, $J = 7.82$ Hz, 2 H), 7.12 (t, $J = 7.38$ Hz, 1 H), 6.14 (s, 1 H), 6.04 (s, 1 H), 5.29 (d, $J = 9.72$ Hz, 2 H), 4.60 (m, 1 H), 4.17 (m, 1 H), 3.06 (m, 1 H), 3.04 (m, 1 H), 2.66 (d.d, $J = 15.84$ and 9.52 Hz, 1 H), 1.37 (d, $J = 6.16$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 168.3$, 165.5, 162.1, 148.0, 142.2, 137.2, 130.8, 129.2, 128.6, 125.1, 124.0, 120.2, 115.7, 66.9, 66.0, 64.8, 55.7, 40.2, 21.6 ppm. HRMS (ESI+) m/z calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_7$: 454.1608; found $[\text{M}+\text{H}]$ 454.2985

(2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((4-methoxyphenylamino)methyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (10)

The crude product was purified by column chromatography (EtOAc/hexane, 80:20; R_f = 0.4) to afford the product (52%) as a semisolid. $[\alpha]_{20}^D = -50.0$ ($c = 0.1$, CHCl_3) ^1H NMR (400 MHz, DMSO): $\delta = 9.87$ (s, 1 H), 8.20 (d, $J = 8.72$ Hz, 2 H), 7.66 (d, $J = 8.72$ Hz, 2 H), 7.40 (d, $J = 9.00$ Hz, 2 H), 6.83 (d, $J = 9.00$ Hz, 2H), 5.83 (d, $J = 9.96$ Hz, 2 H), 5.31 (s, 2 H), 5.03 (d, $J = 4.40$ Hz, 2 H), 4.53-4.49 (m, 1 H), 3.97 (q, $J = 16.24$, and 5.44 Hz, 1 H) 1 H), 3.69 (s, 3 H), 3.11 (dd, $J = 5.30$ and 2.38 Hz, 1 H), 2.77-2.69 (m, 2H), 1.10 (d, $J = 6.32$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 167.5$, 166.0, 161.8, 155.2, 147.1, 143.2, 131.9, 131.5, 128.5, 123.5, 120.7, 113.7, 113.5, 65.4, 63.4, 62.7, 55.0, 40.1, 21.6 ppm. HRMS (ESI+) m/z calcd. for $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_8$: 484.1714; found $[\text{M}+\text{H}]$ 484.1712

(2*S*,5*R*,6*S*)-4-nitrobenzyl 2-((4-bromophenylamino)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (11)

The crude product was purified by column chromatography (ethylacetate /hexane, 80:20; R_f = 0.4) to afford the product (50%) as a semisolid. $[\alpha]_{20}^D = -70.0$ ($c = 0.1$, CHCl_3) ^1H NMR (400 MHz, CDCl_3): $\delta = 8.23$ (d, $J = 8.52$ Hz, 2 H), 7.78 (s, 1 H), 7.52 (d, $J = 8.52$ Hz, 2 H), 7.41-7.35(m, 4H), 6.17 (s,1H), 6.06 (s,1H), 5.29 (q, $J = 19.74$ and 47.06 Hz, 2 H), 4.61-4.59 (m, 1 H), 4.20-4.16 (m, 1 H), 3.06 (dd, $J = 19.26$ and 11.34 Hz, 1 H), 2.68-2.64 (m, 2H), 1.37 (d, $J = 6.12$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta =$

168.2, 165.4, 162.1, 148.0, 142.1, 136.3, 132.2, 130.7, 128.6, 124.1, 121.7, 117.7, 115.8, 66.9, 64.7, 55.6, 40.4, 21.6 ppm. HRMS (ESI-) m/z calcd. for $C_{23}H_{22}BrN_3O_7$: 530.0557; found [M-H] 530.0612

General Procedure for Michael reaction

To a stirred solution of compound **1** (1.0 eq) and catalyst (0.2 eq) in DMSO (0.5 mL) at room temperature, was added Michael acceptor (2.0 eq). The mixture was stirred at ambient temperature for 24 h while being monitored by TLC. The reaction mixture was then quenched by adding water (5 mL) and the aqueous layer was extracted three times with DCM (30 mL). The combined organic layers were dried with Mg_2SO_4 which was subsequently removed by filtration. The concentrated extract was subjected to silica gel for purification to afford the desired product.

(2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (12**)**

The crude product was purified by column chromatography (ethylacetate /hexane, 50:50; R_f = 0.2) to afford the product (124 mg, 41%) as a semi solid. $[\alpha]_{20}^D = +156.7$ (c = 0.1, $CHCl_3$) 1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.60 Hz, 2H), 7.48 (d, J = 8.60 Hz, 2H), 7.21 (d, J = 8.68 Hz, 2H), 6.82 (d, J = 8.72 Hz, 2H), 5.32 (m, 2H), 5.00 (dd, J = 13.17, 11.17 Hz, 2H), 4.36 (dd, J = 11.11, 4.10 Hz, 1H), 4.10 (m, 1H), 3.56 (m, 1H), 3.12 (dd, J = 5.20, 2.56 Hz, 1H), 2.43 (dd, J = 8.80, 8.72 Hz, 1H), 2.27 (dd, J = 6.88, 6.96 Hz, 1H), 1.29 (d, J = 6.28 Hz, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ 207.3, 171.5, 164.9, 160.9, 141.7, 131.7, 129.1, 124.1, 114.5, 94.5, 74.3, 67.3, 67.1, 55.4, 55.0, 51.1, 44.1, 40.5, 21.2 ppm. HRMS (ESI+) m/z calcd. for $C_{25}H_{25}N_3O_{10}$: 528.1612; found [M+H] 528.3154

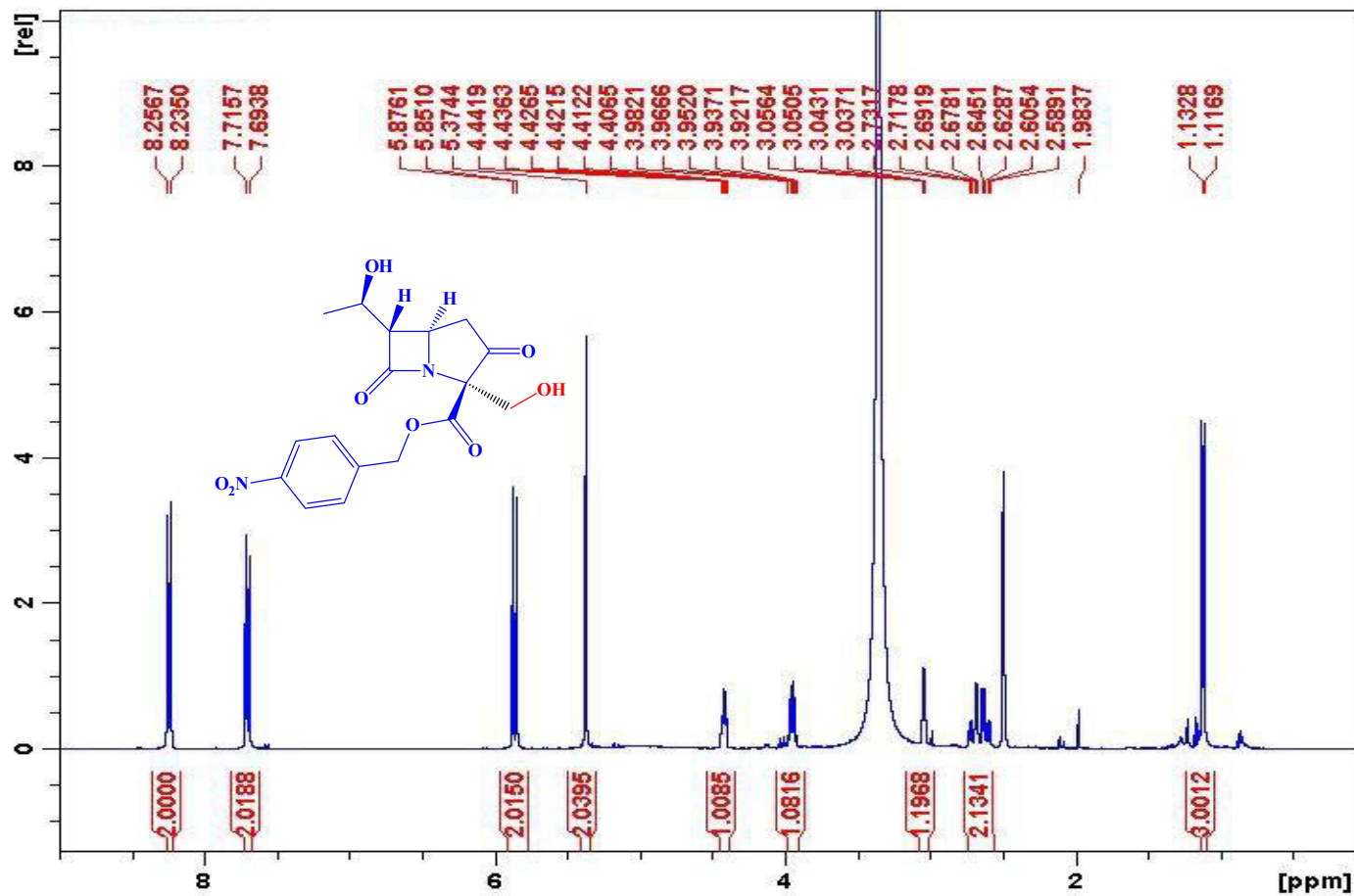
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The crude product was purified by column chromatography (ethylacetate /hexane, 50:50; R_f = 0.2) to afford the product (165 mg, 67%) as a semi solid. $[\alpha]_{20}^D = +215.0$ (c = 0.1, $CHCl_3$) 1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 7.16 Hz, 2H), 7.45 (d, J = 8.56 Hz, 2H), 5.27 (s, 2H), 4.25 (s, 1H), 4.03 (s, 1H),

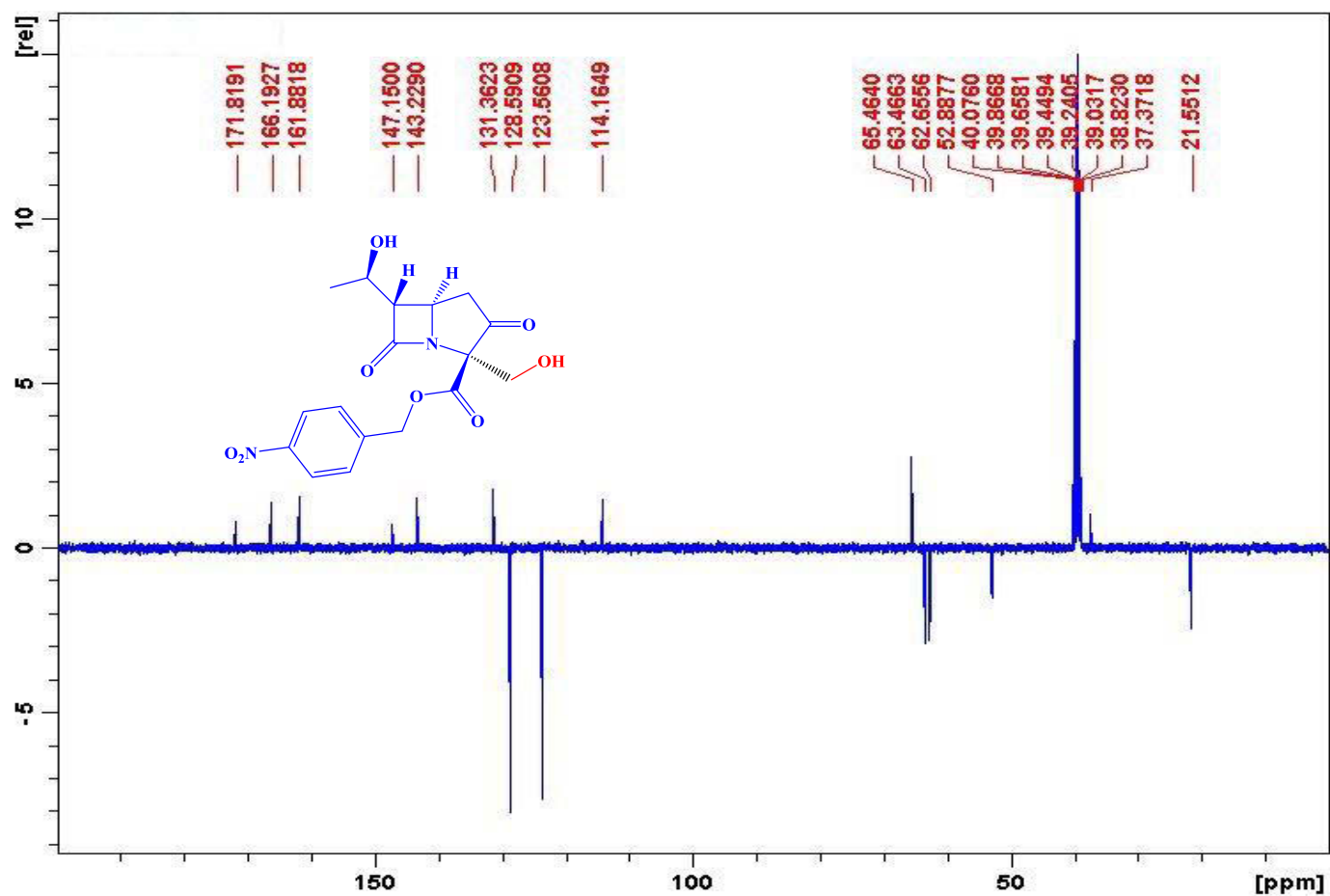
3.29 (t, 1H), 3.17 (d, 1H), 2.97- 2.95 (d, $J = 11.05$ Hz, 1H), 2.55- 2.39 (dd, $J = 17.91, 8.58$ Hz, 2H), 2.19 (d, $J = 9.49$ Hz, 2H), 2.04 (d, $J = 7.08$ Hz, 1H), 1.80 (d, $J = 19.61$ Hz, 1H), 1.34 (d, $J = 4.80$ Hz, 3H) ppm. ^{13}C NMR (100 MHz CDCl_3): δ 215.3, 208.0, 164.9, 161.0, 140.8, 128.7, 124.5, 76.6, 66.5, 66.2, 64.9, 50.2, 42.1, 40.9, 38.4, 38.0, 23.6, 21.9 ppm. HRMS (ESI-) m/z calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_8$: 429.1292; found [M-H] 429.1440

¹H, ¹³C NMR and HRMS spectra

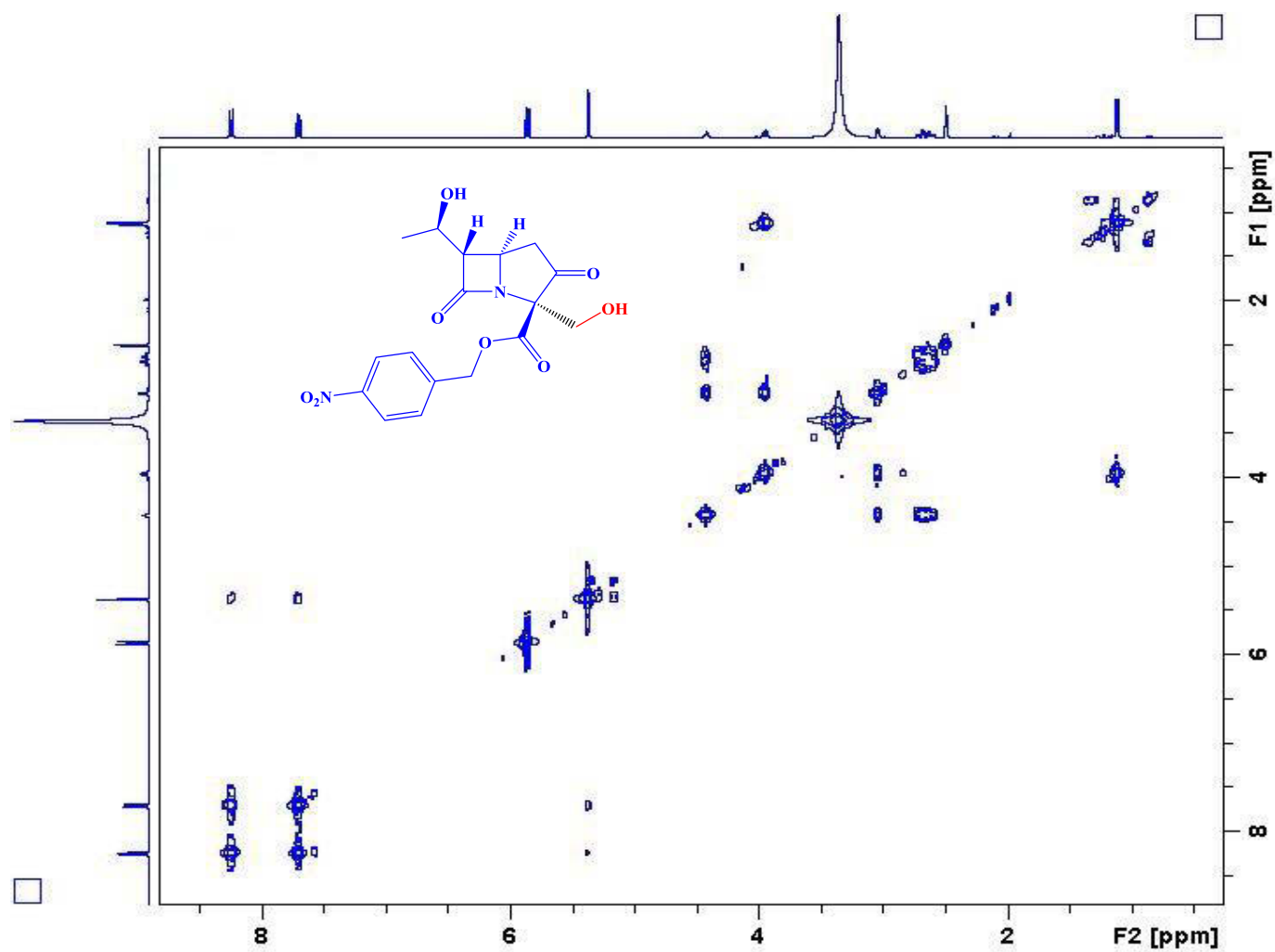
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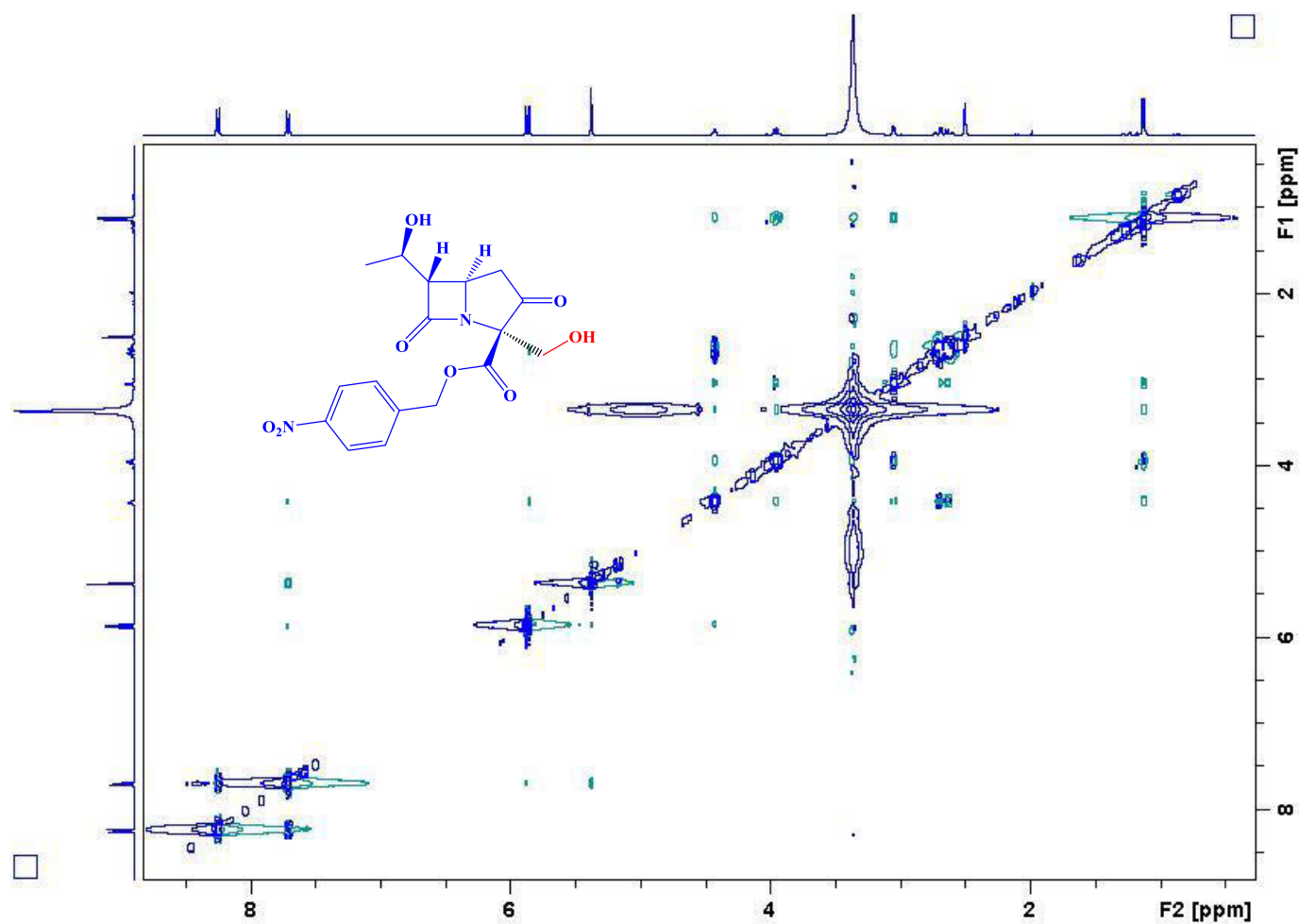
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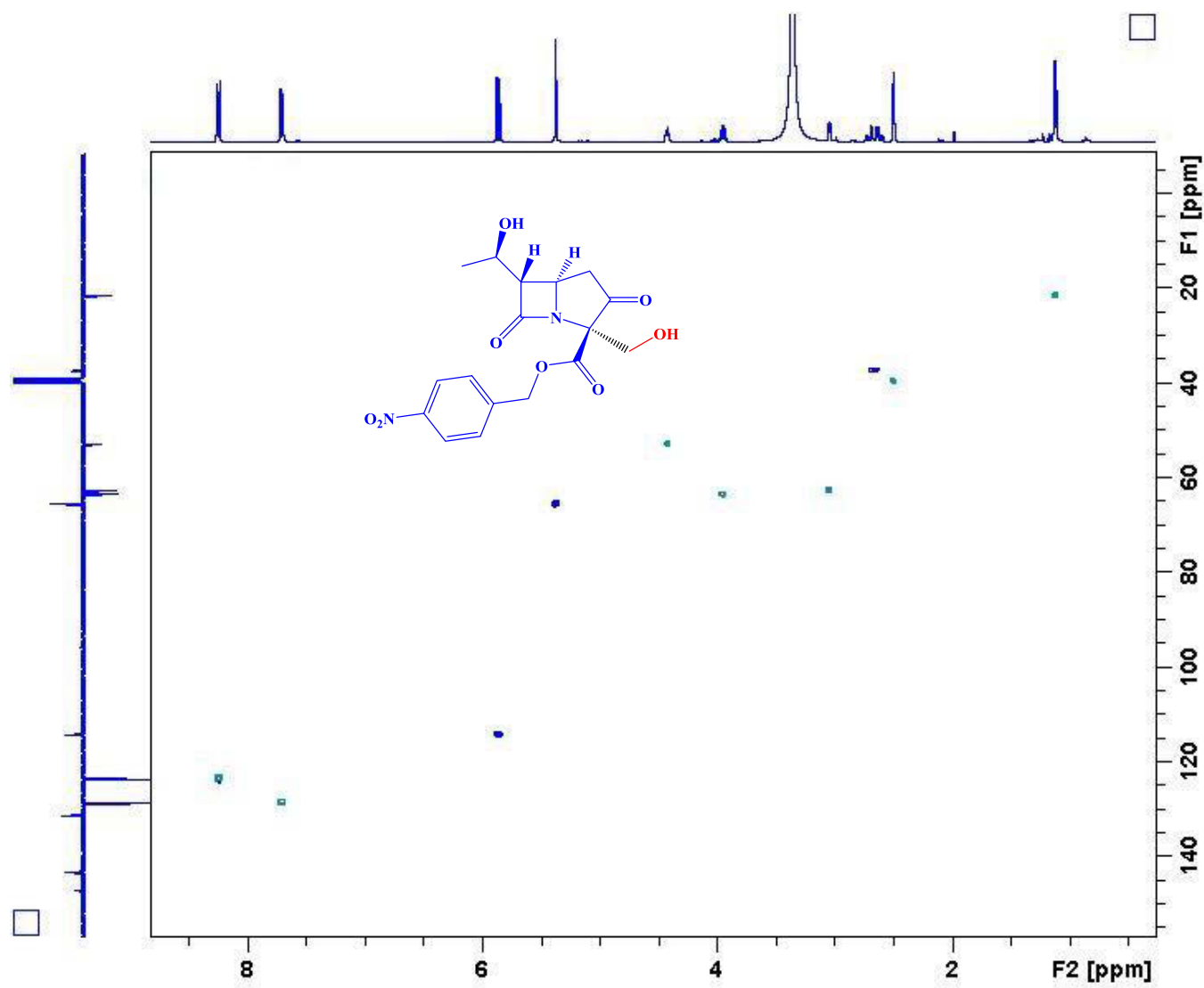
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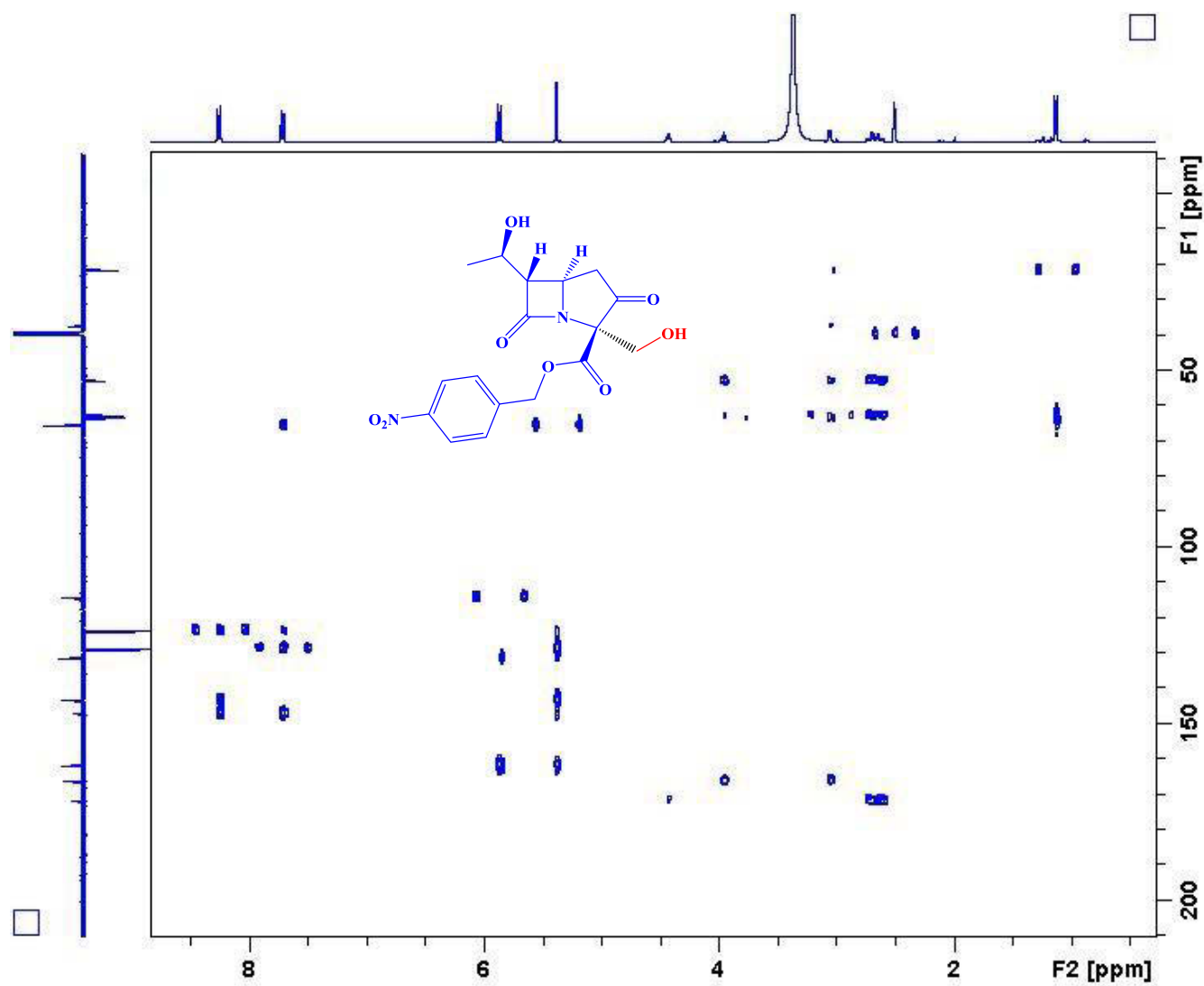
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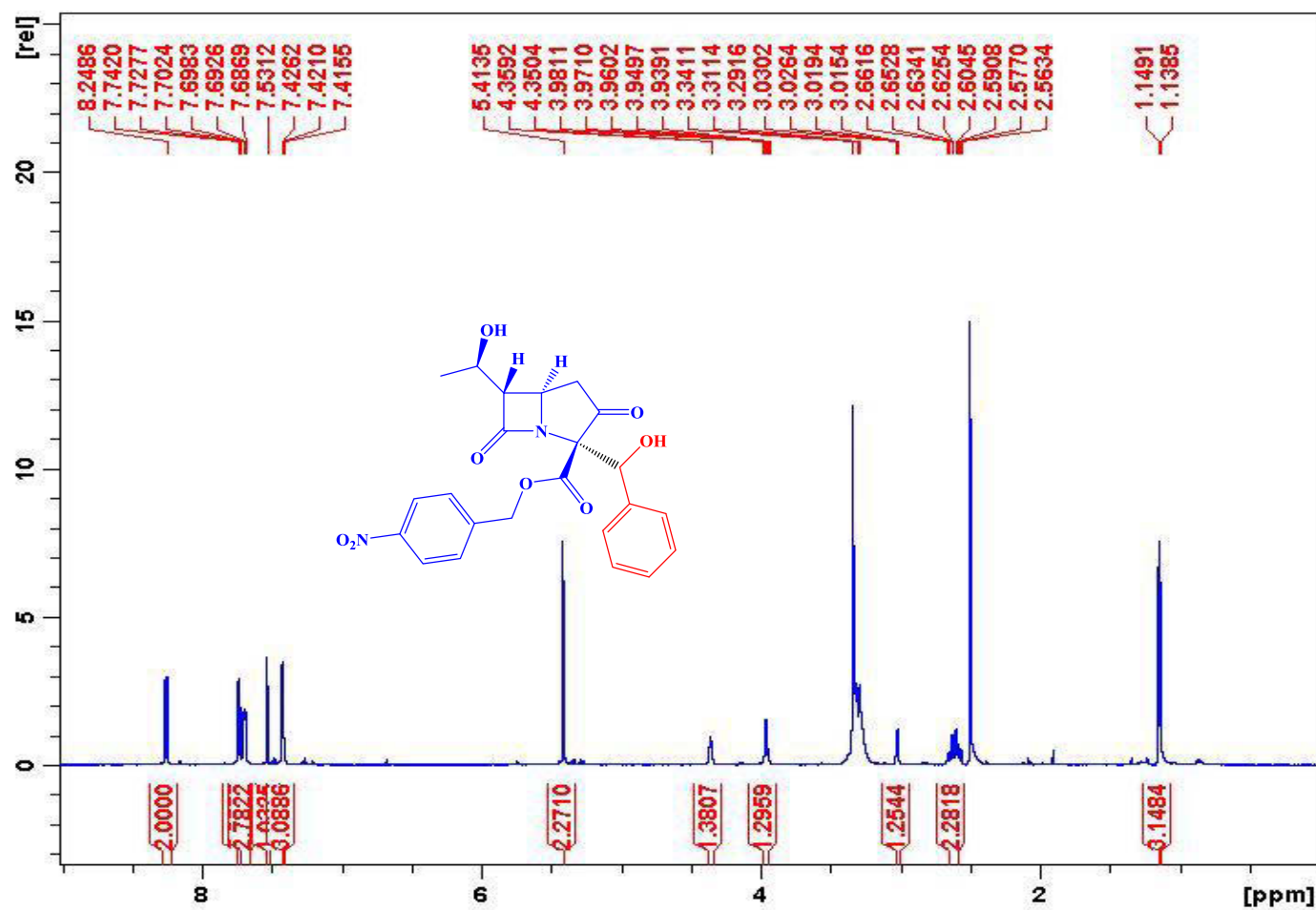
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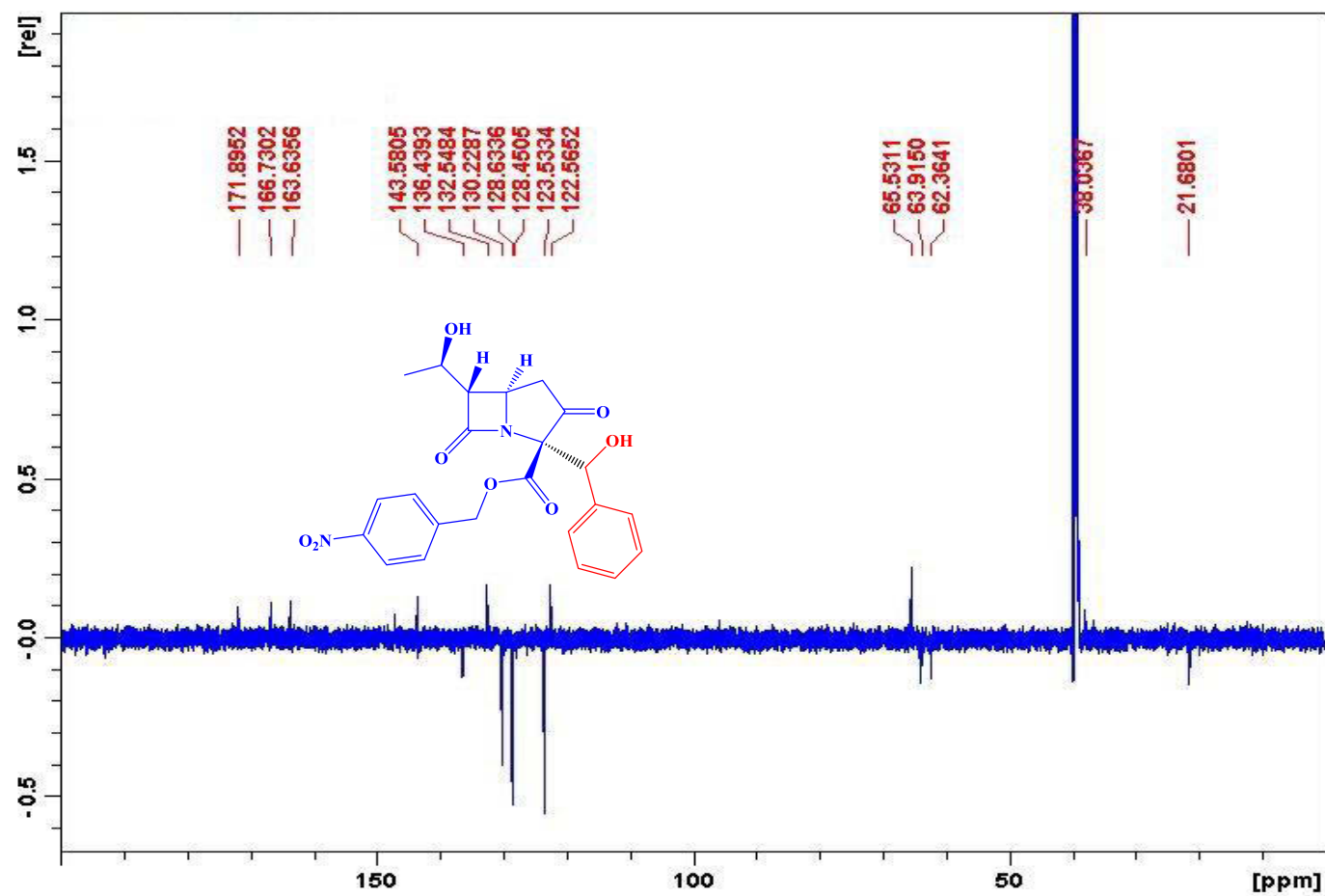
HMBC of ((2*S*)-4-nitrobenzyl-6-((*R*)-1-hydroxyethyl)-2-(hydroxymethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (2)



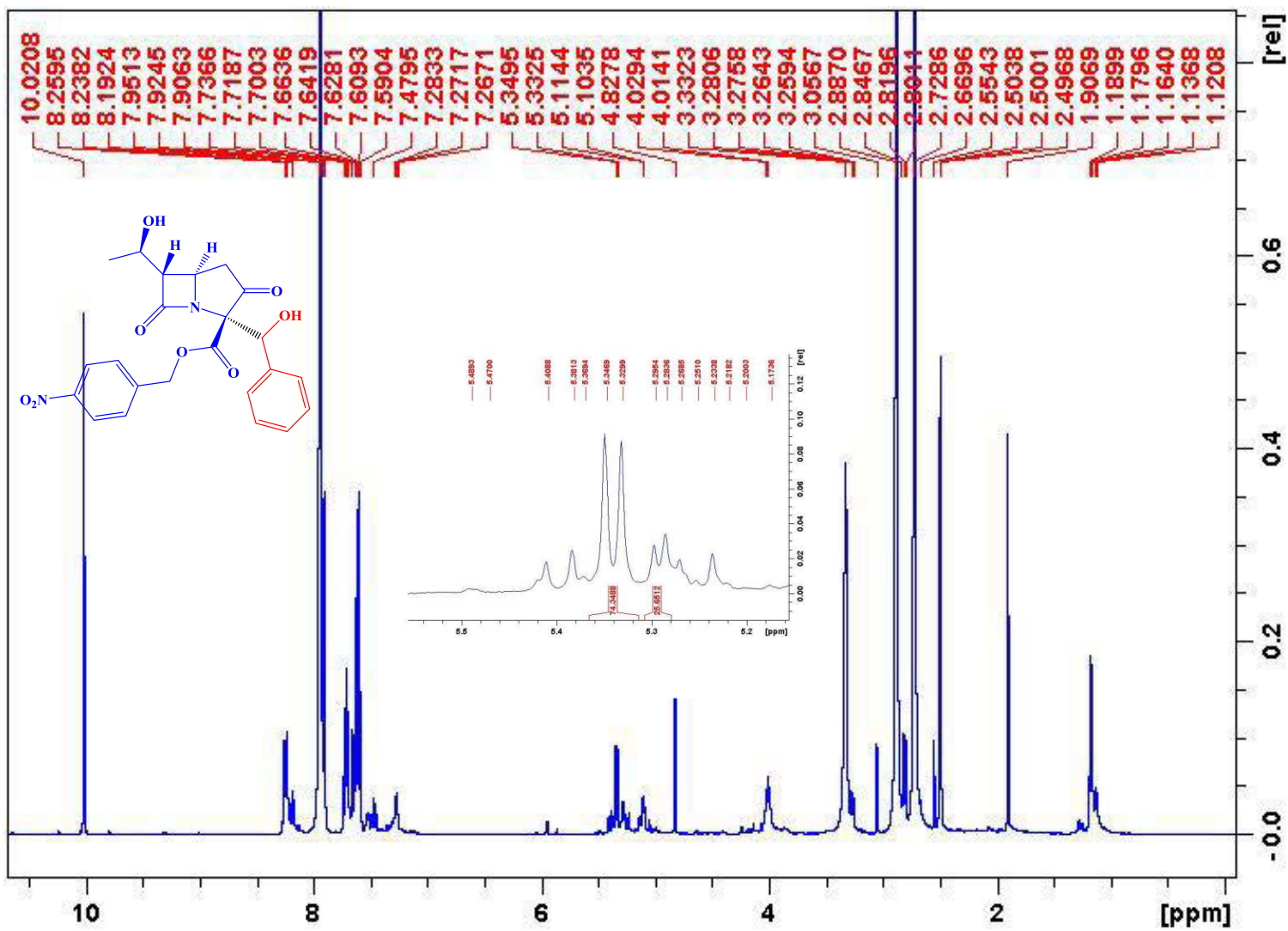
¹H-NMR spectra of (2*S*)-nitrobenzyl-2-((*R*)-hydroxy(phenyl)methyl)-6-(1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3)



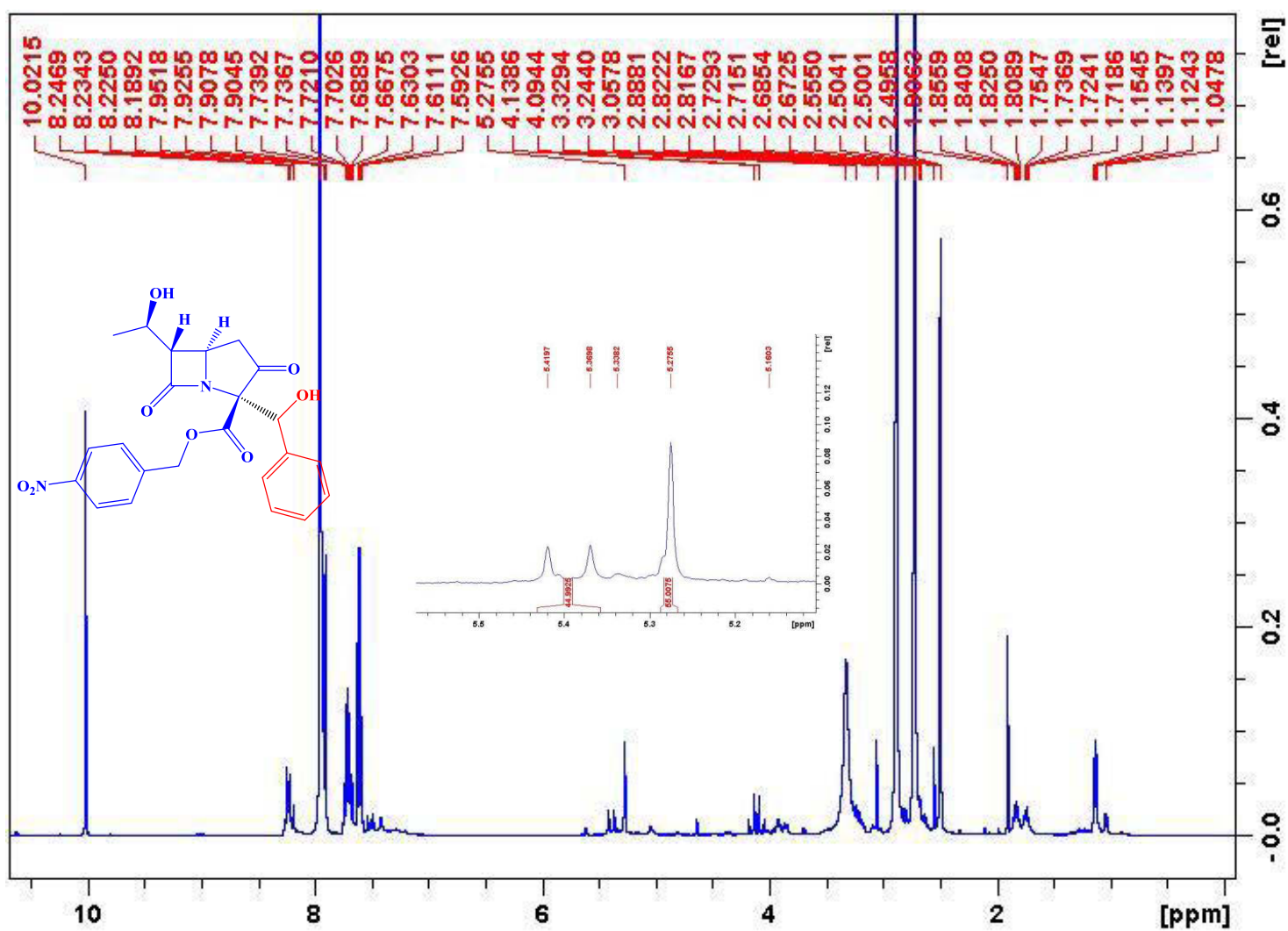
^{13}C -NMR spectra of (2*S*)-nitrobenzyl2-((*R*)-hydroxy(phenyl)methyl)-6-(1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3)



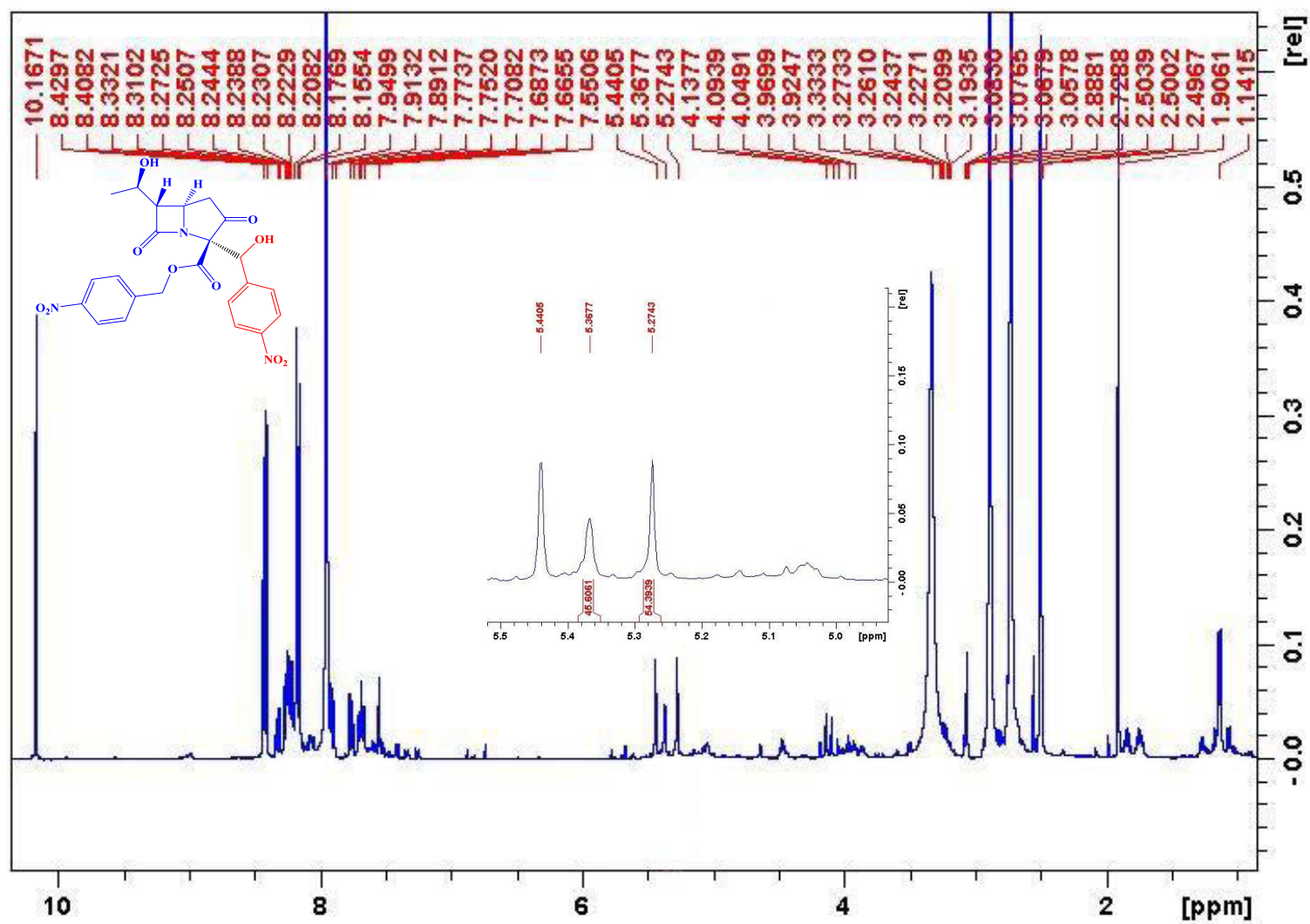
Crude ^1H -NMR spectra of (2S)-nitrobenzyl2-((R)-hydroxy(phenyl)methyl)-6-(1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3)



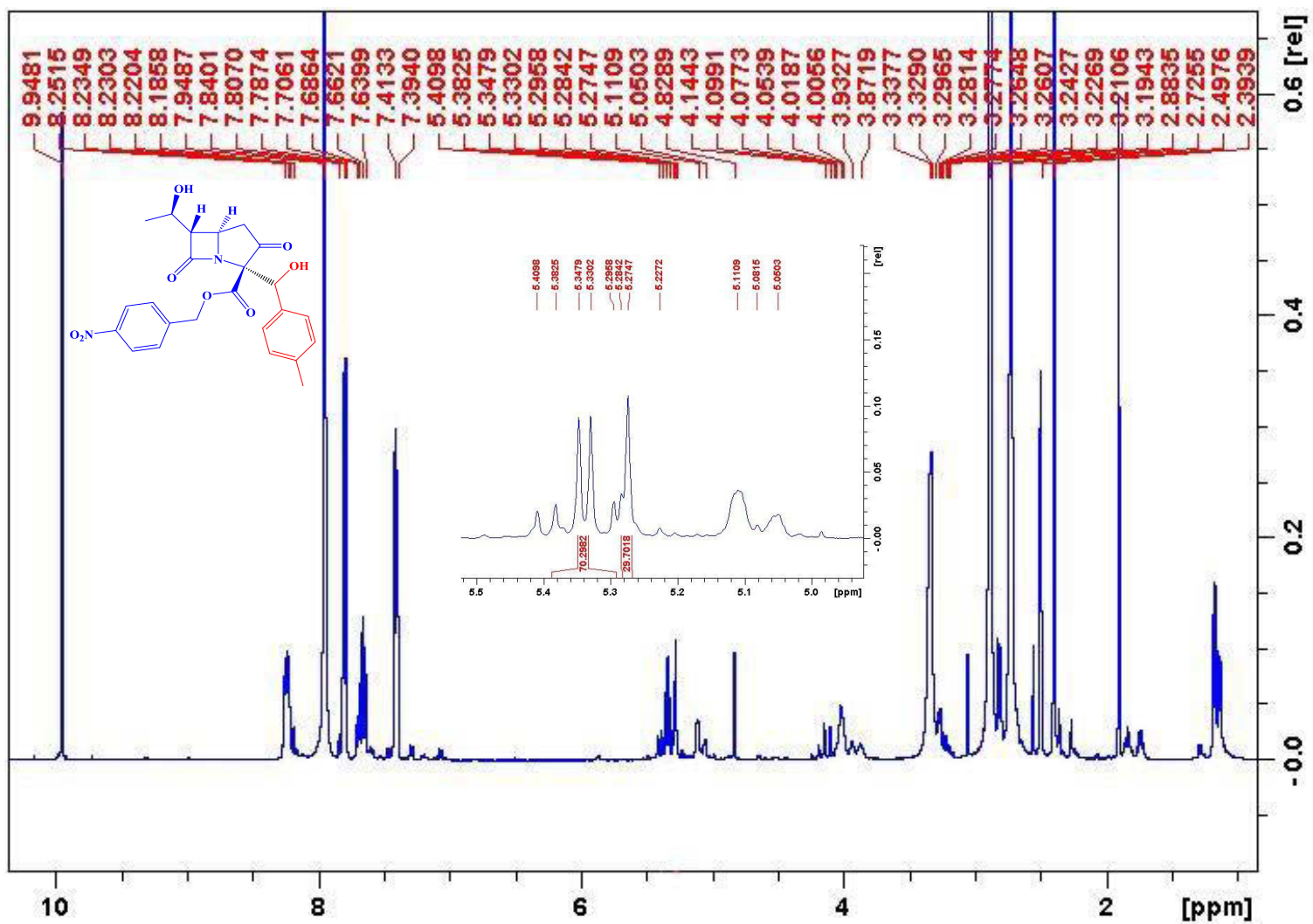
Crude ^1H -NMR spectra of (2S)-nitrobenzyl2-((R)-hydroxy(phenyl)methyl)-6-(1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3)



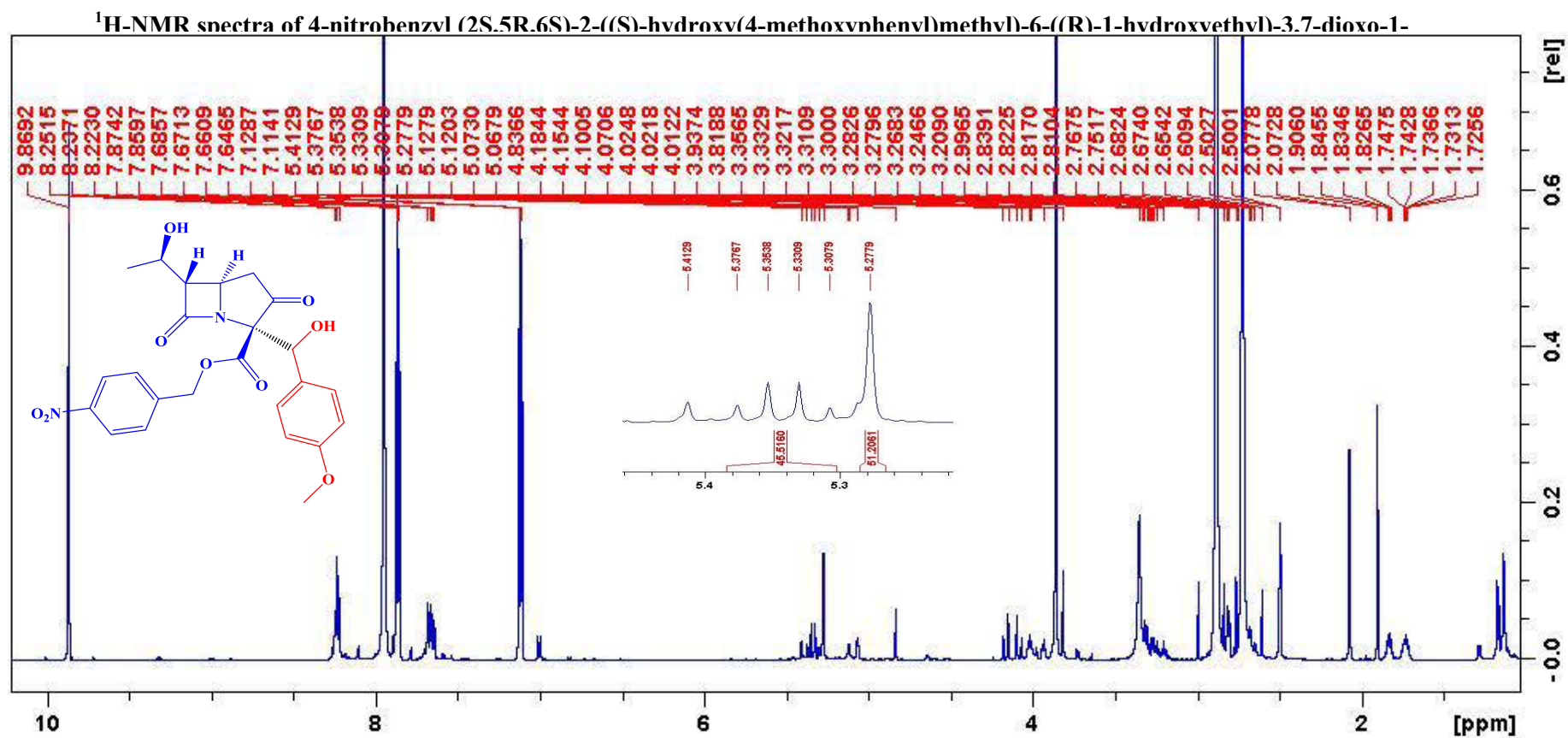
Crude ^1H -NMR spectra of 4-nitrobenzyl (2*S*,5*R*,6*S*)-2-((*S*)-hydroxy(4-nitrophenyl)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (4)

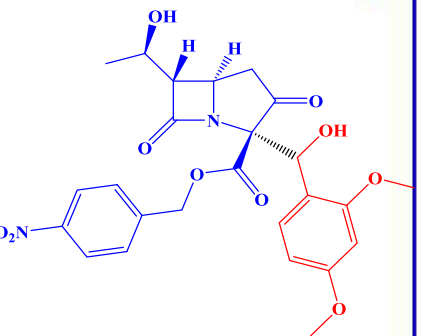


Crude ^1H -NMR spectra of 4-nitrobenzyl (2*S*,5*R*,6*S*)-2-((*S*)-hydroxy(*p*-tolyl)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5)

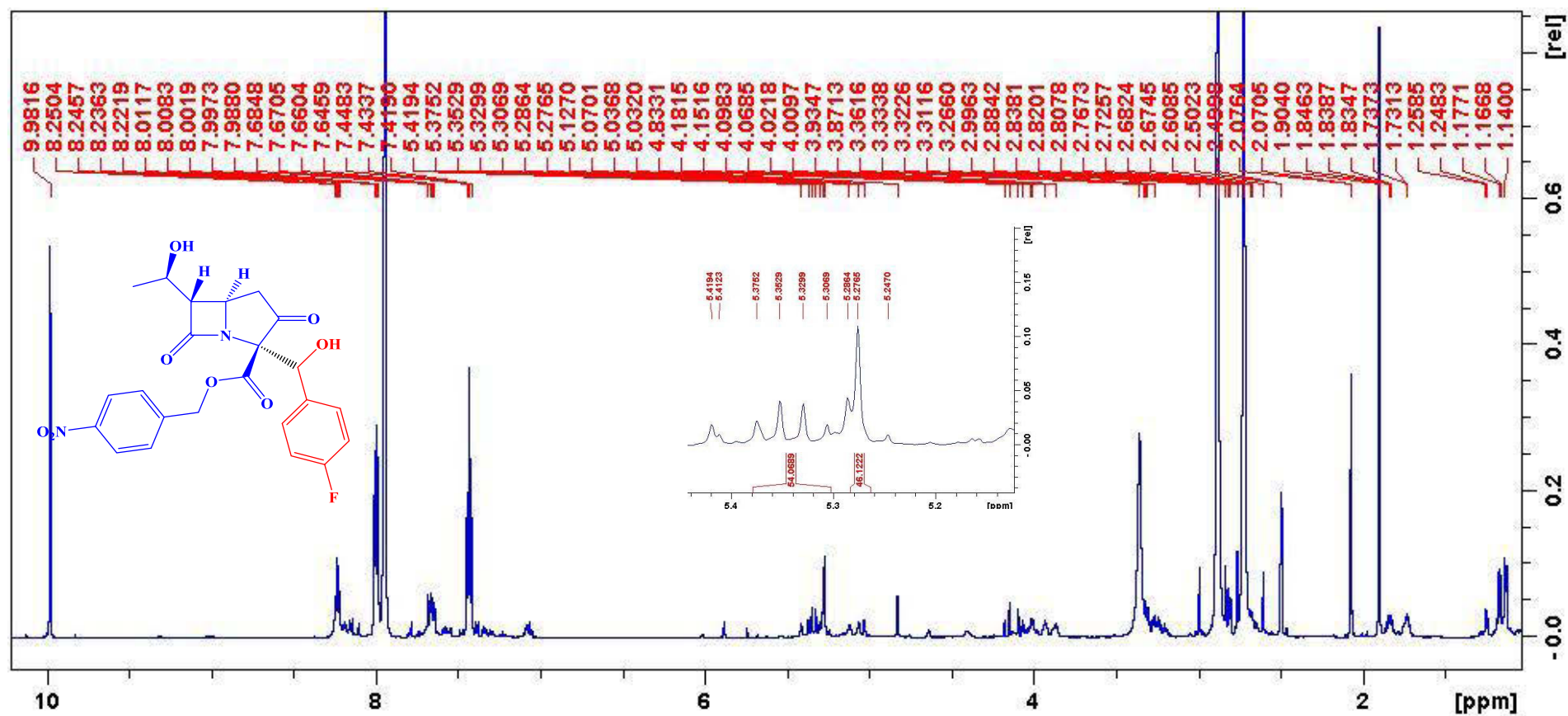


Crude ^1H -NMR spectra of 4-nitrobenzyl (2*S*,5*R*,6*S*)-2-((*S*)-hydroxy(4-methoxyphenyl)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (6)

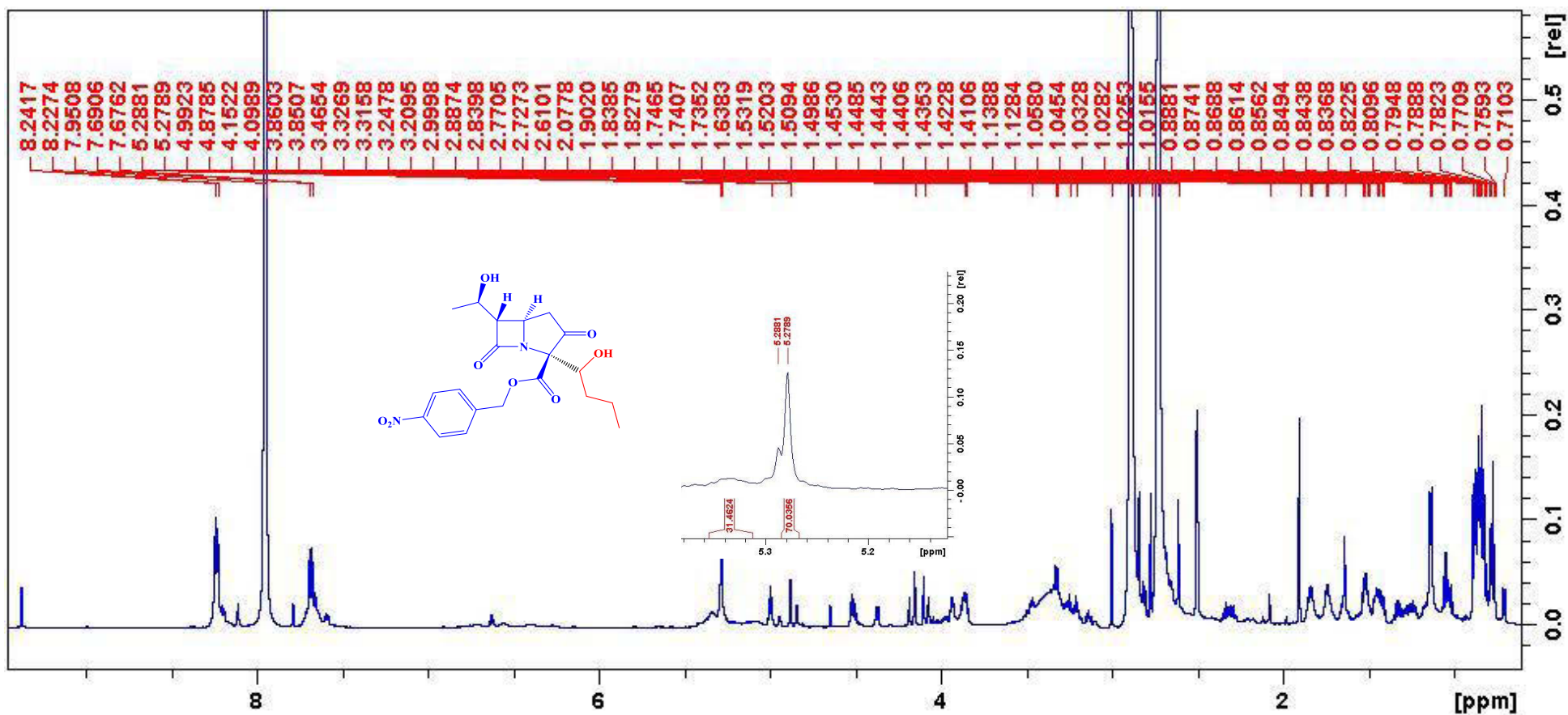


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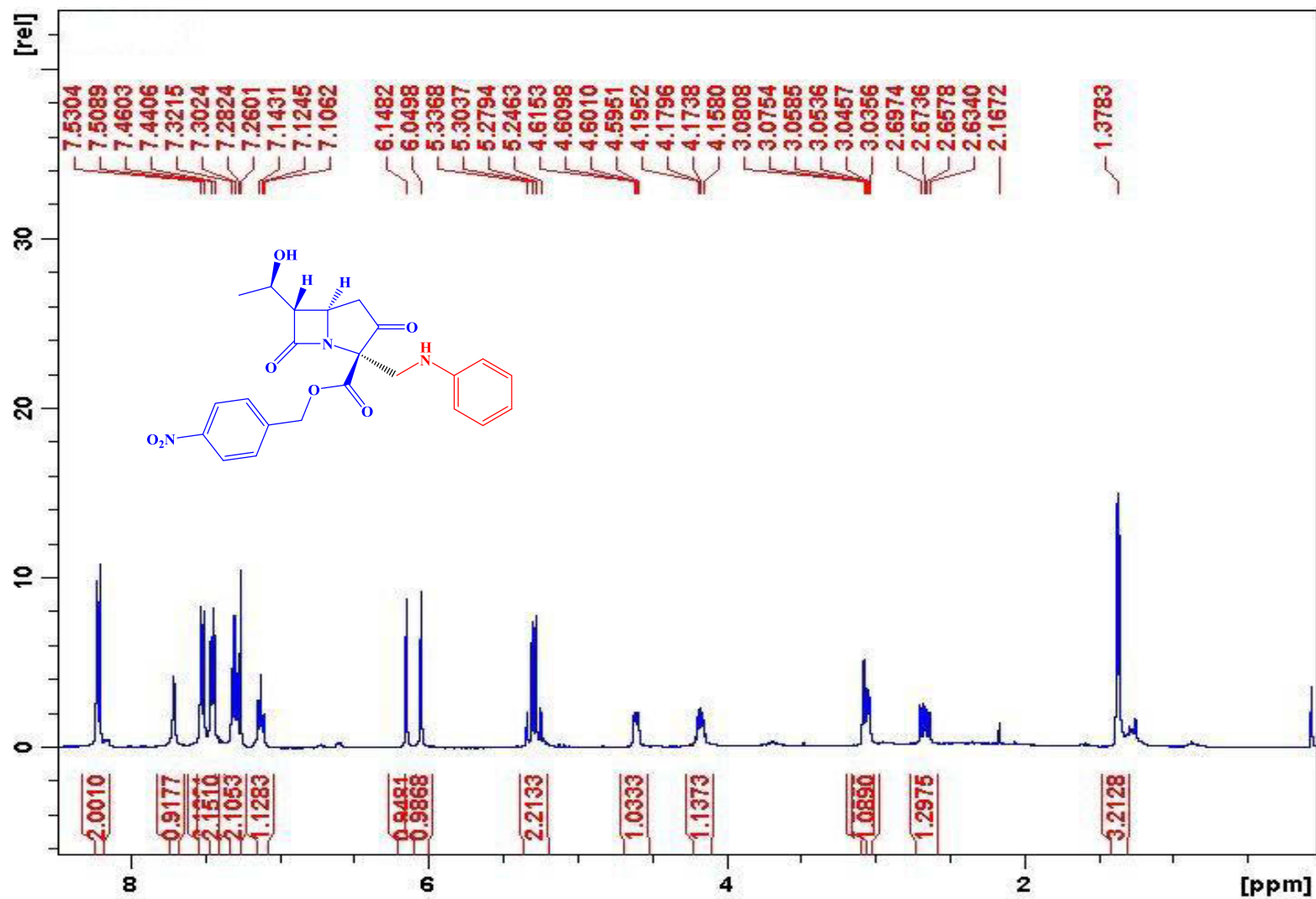
Crude ^1H -NMR spectra of 4-nitrobenzyl (2*S*,5*R*,6*S*)-2-((*S*)-(4-fluorophenyl)(hydroxy)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (7)



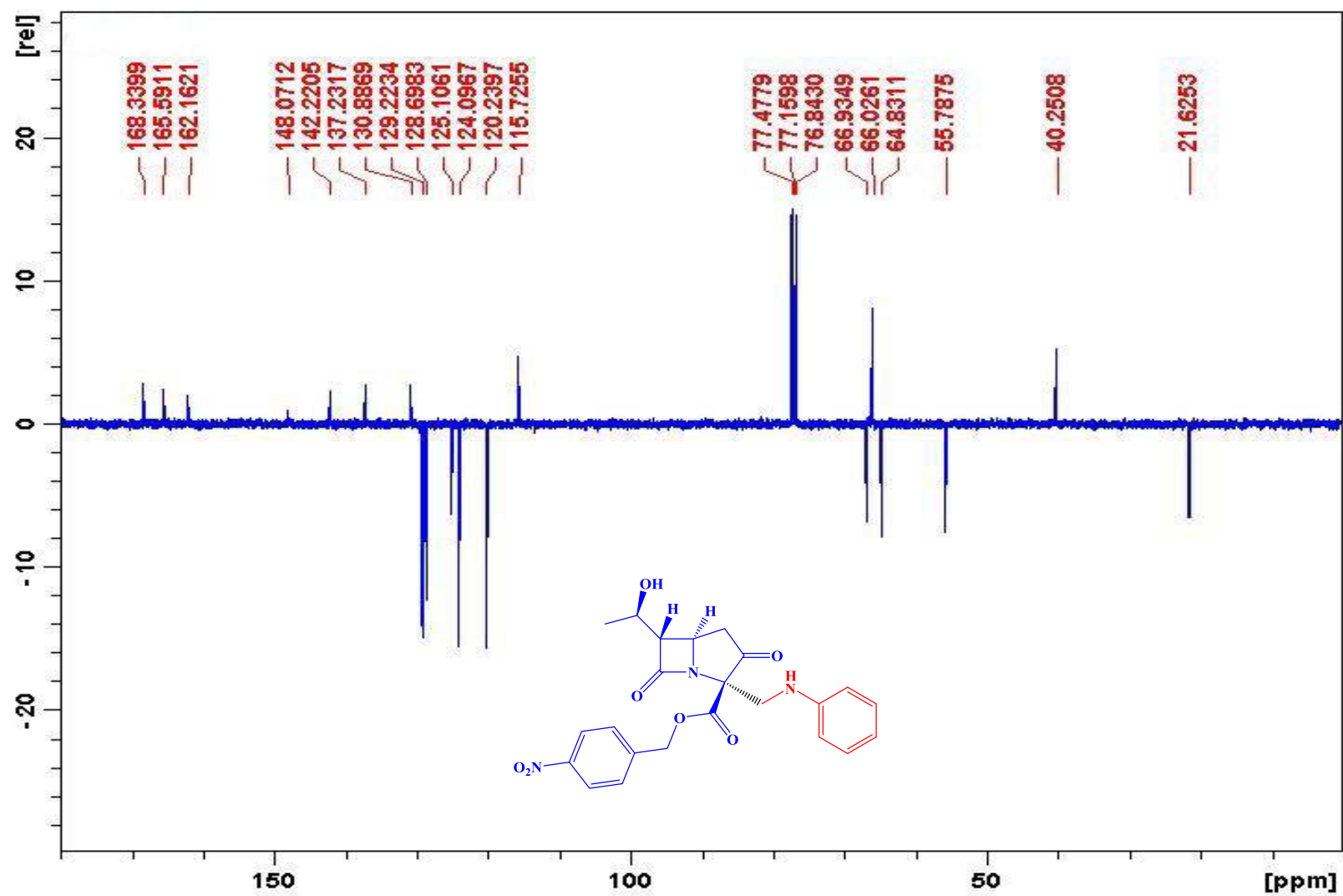
Crude ^1H -NMR spectra of 4-nitrobenzyl (2*S*,5*R*,6*S*)-2-((*S*)-1-hydroxybutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (8)



¹H-NMR spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((phenylamino)methyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (9)

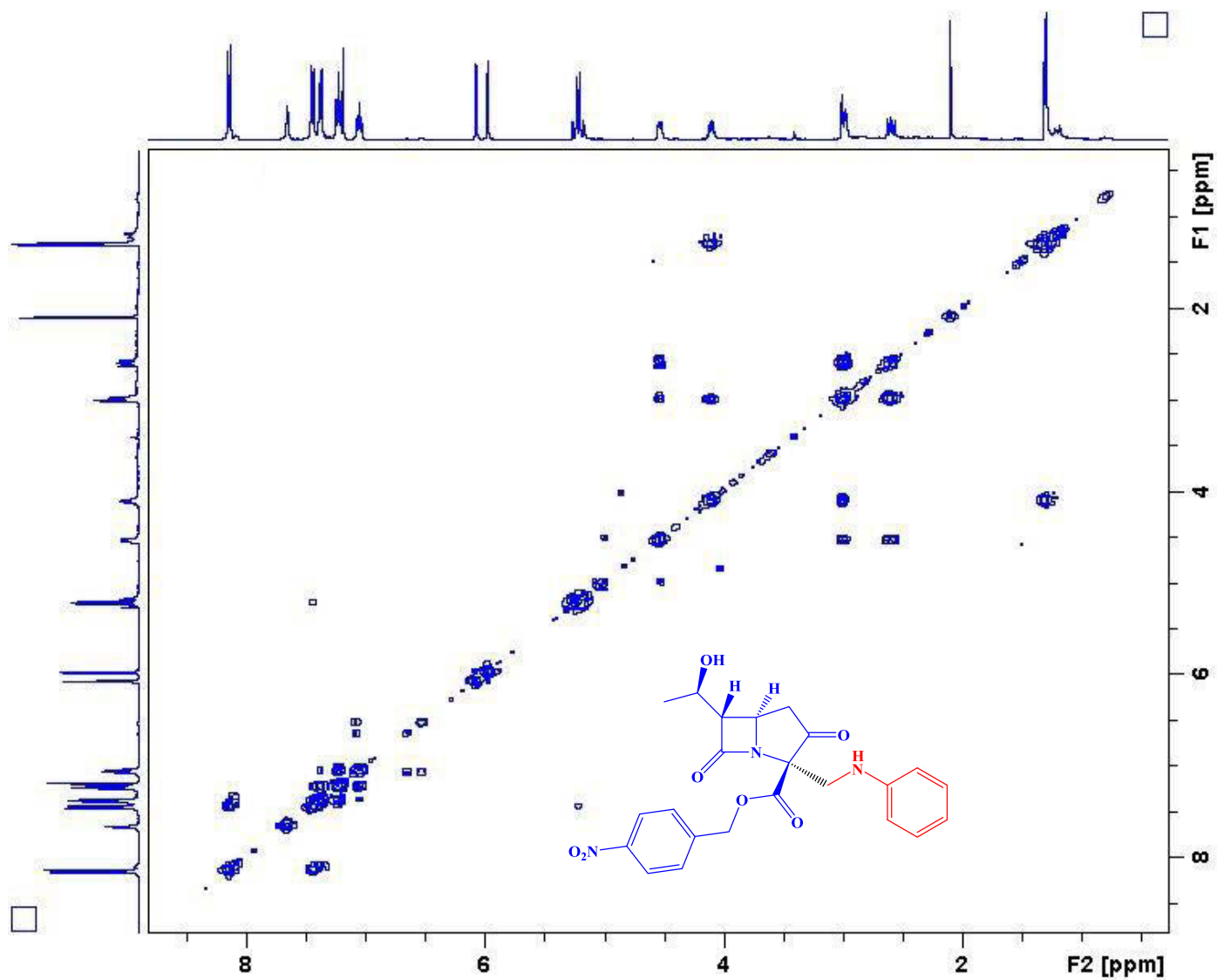


^{13}C -NMR spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((phenylamino)methyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (9)

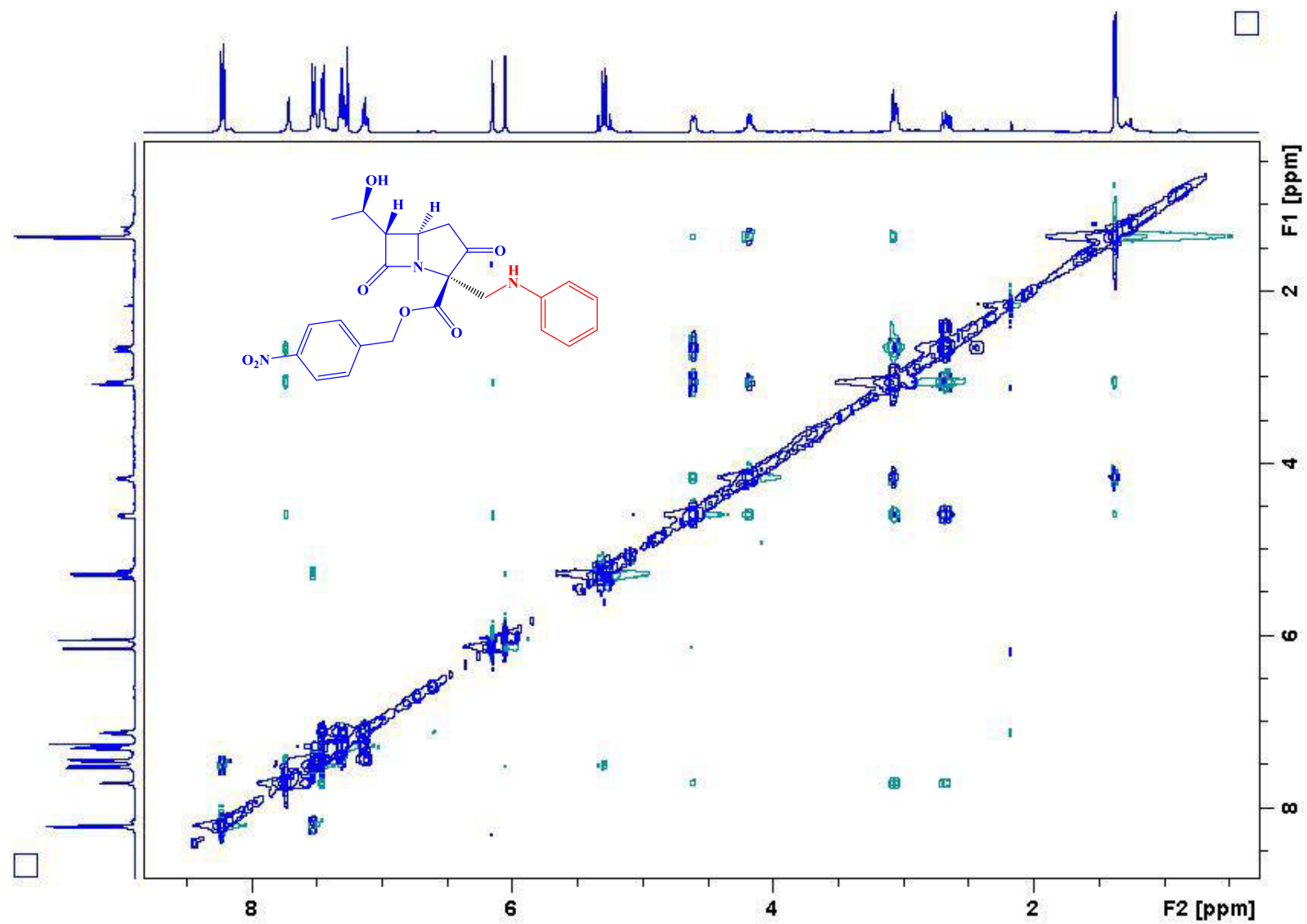


COSY of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((phenylamino)methyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate

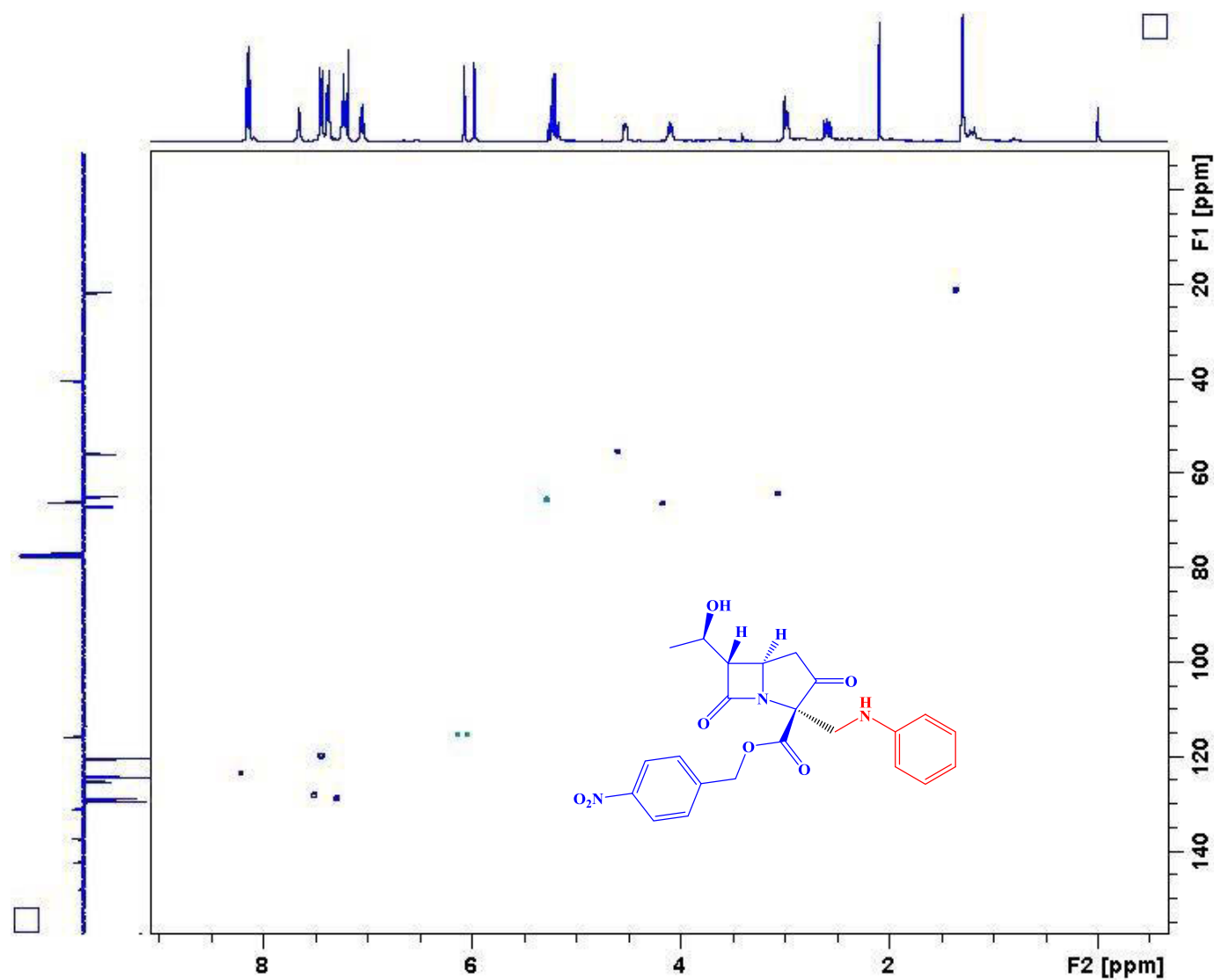
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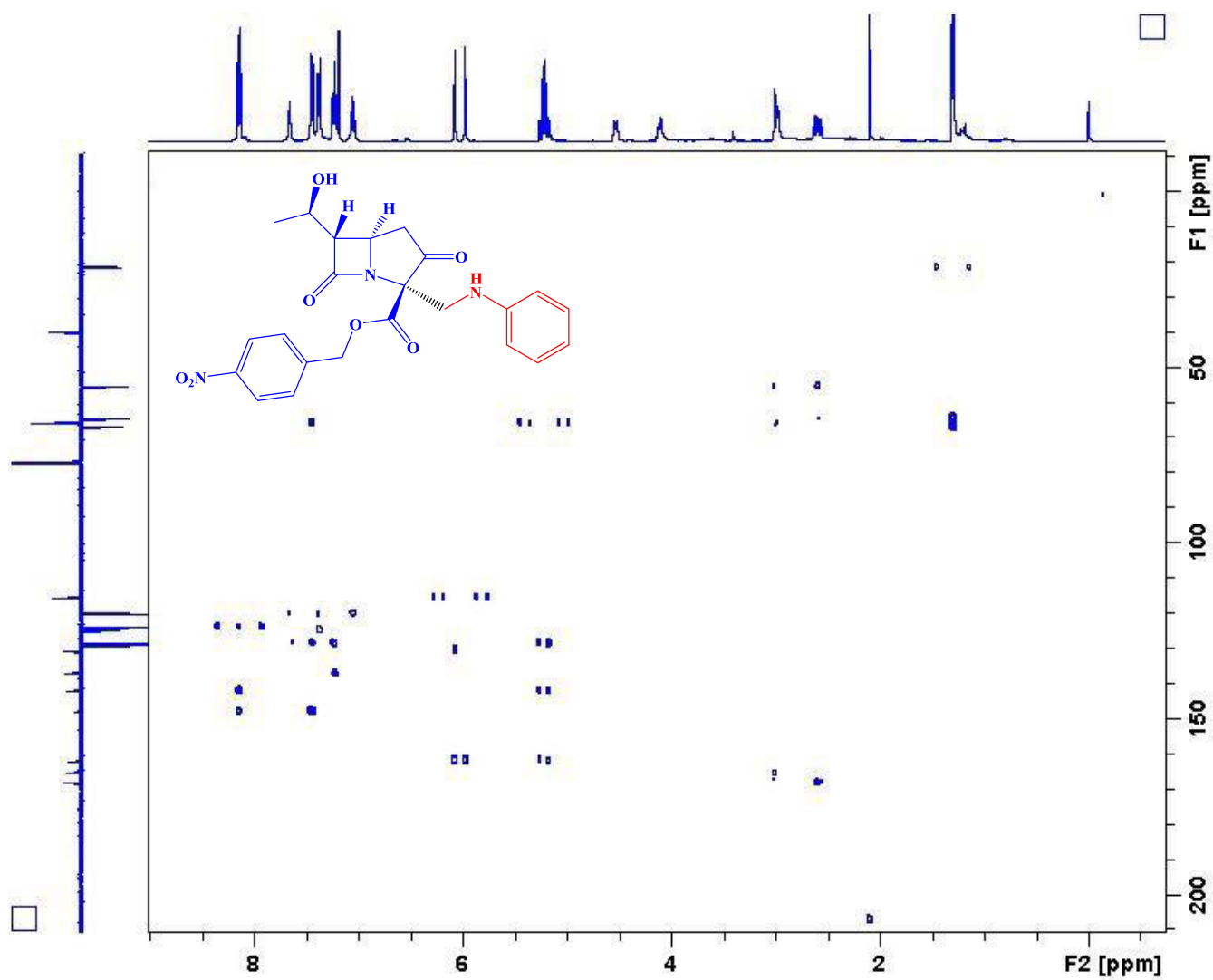
NOESY of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((phenylamino)methyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate



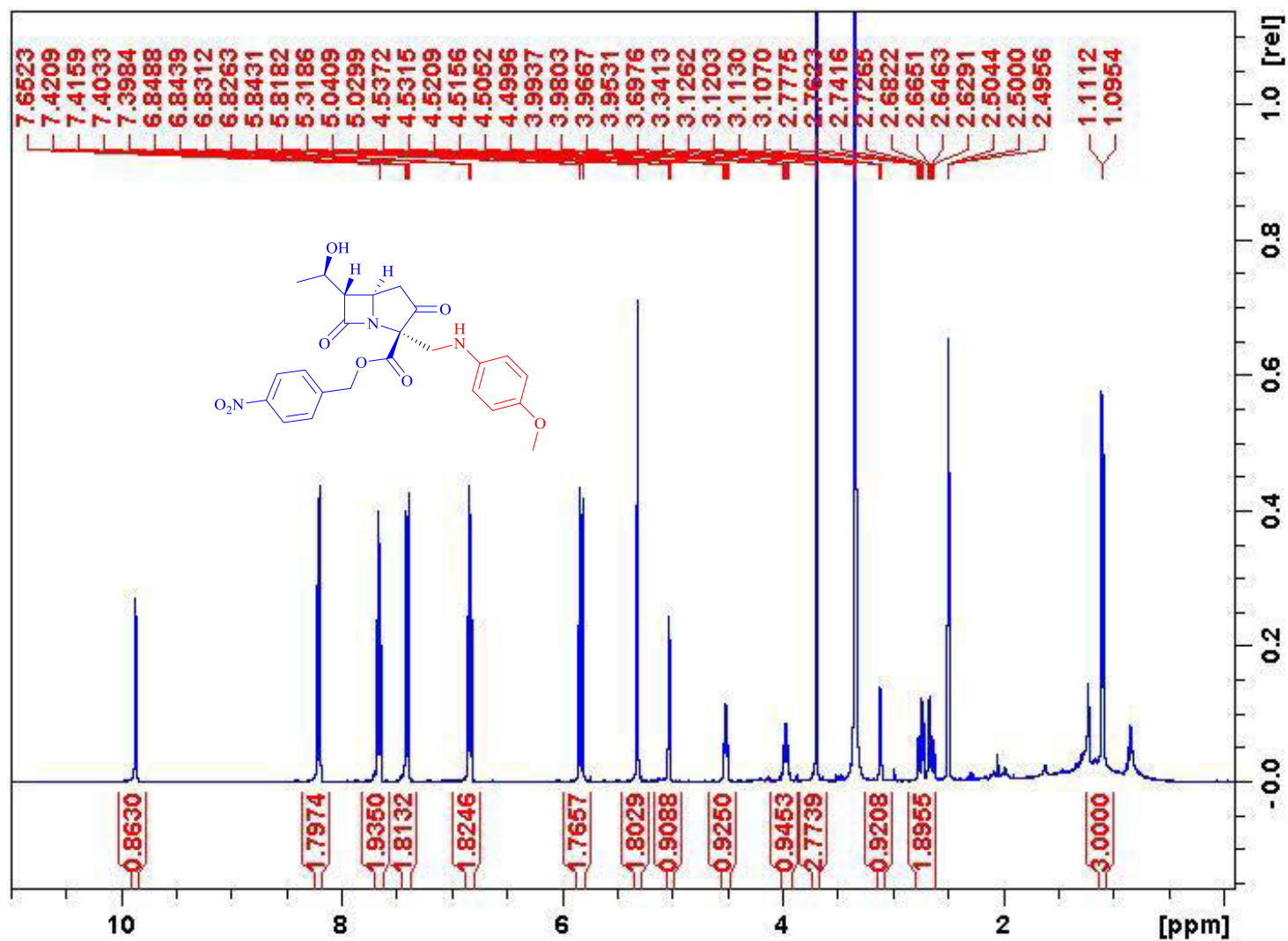
HSQC of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((phenylamino)methyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate
(9)



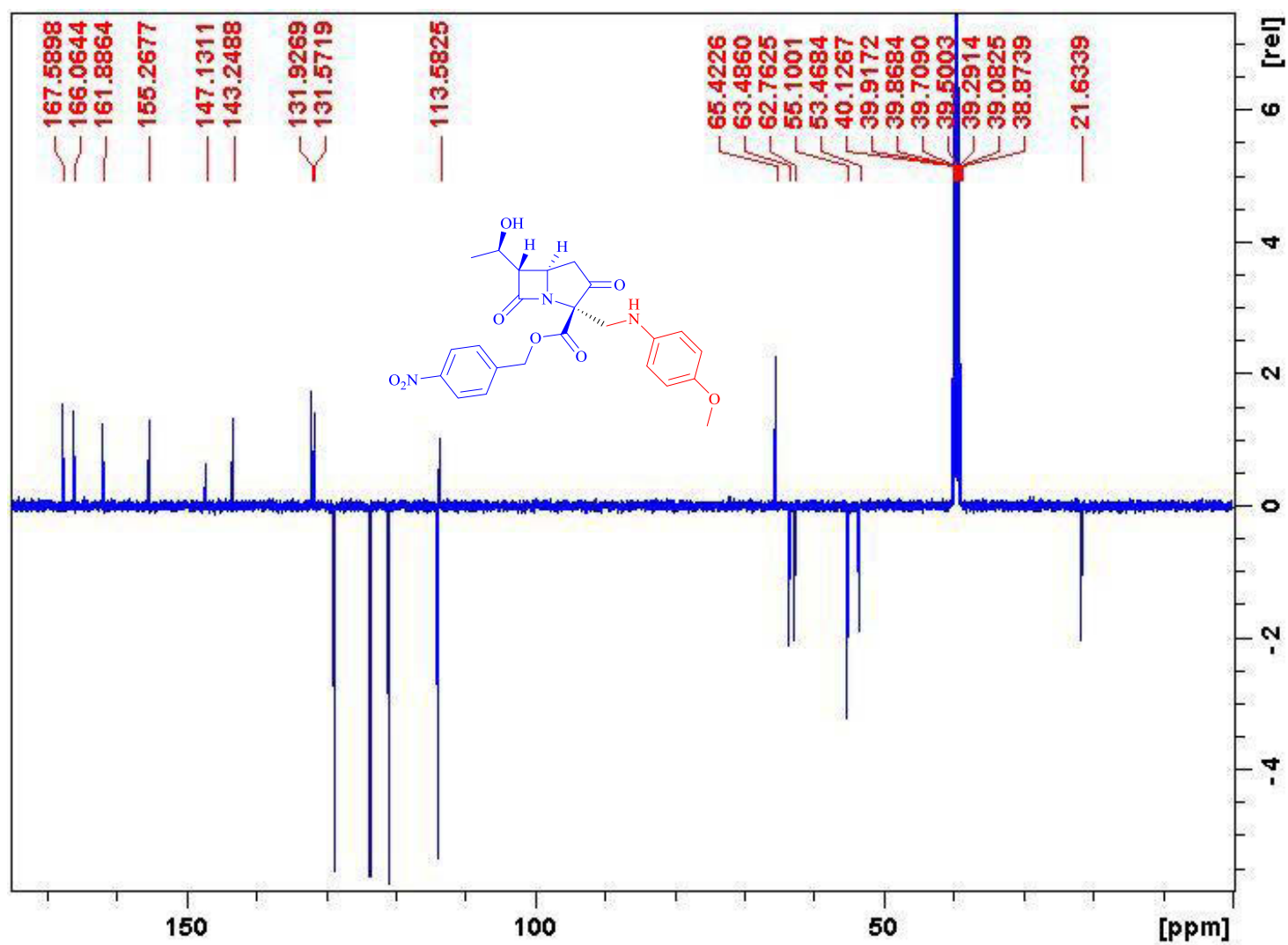
HMBC of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((phenylamino)methyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate
(9)



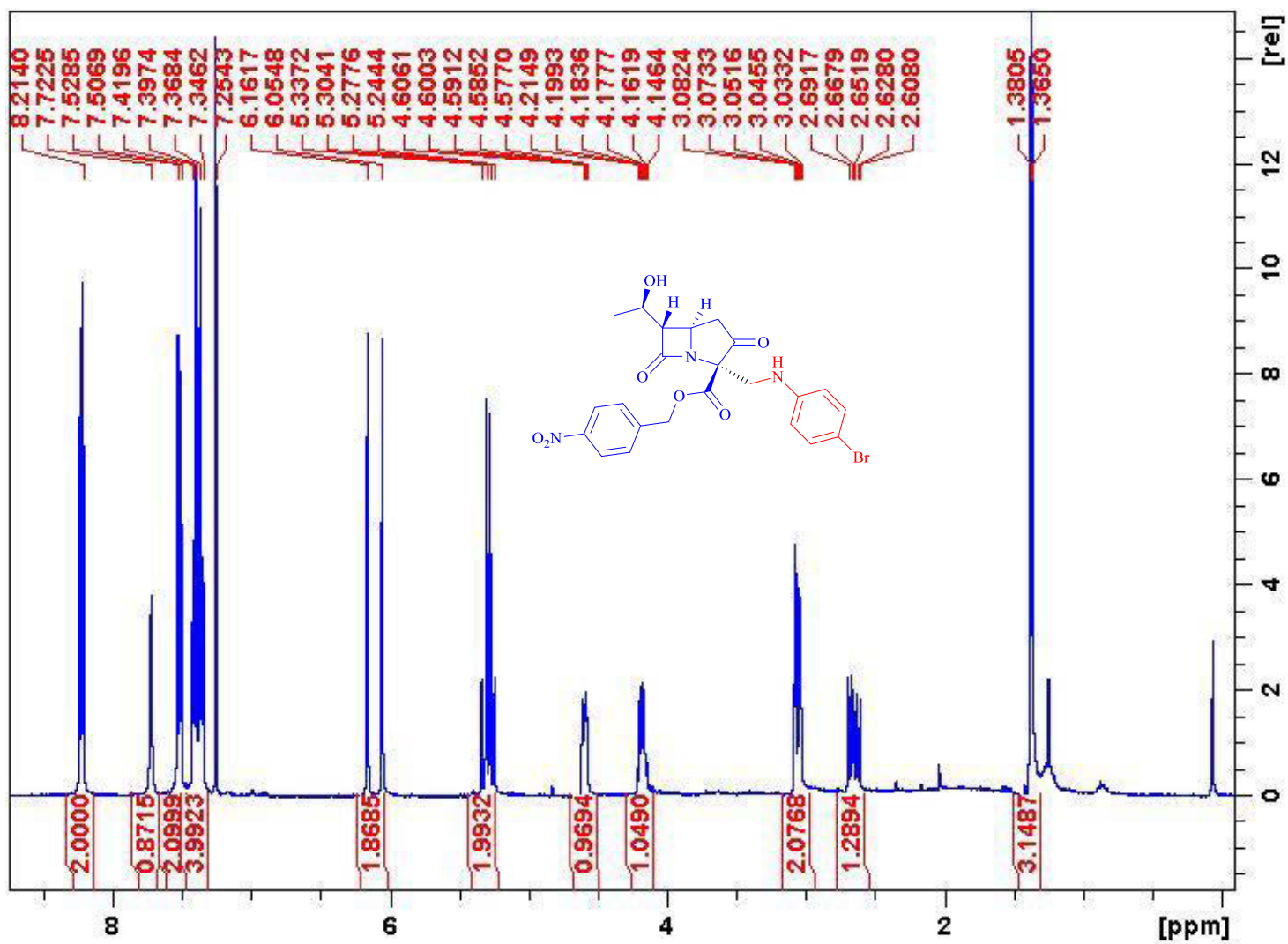
¹H-NMR spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((4-methoxyphenylamino)methyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (10)



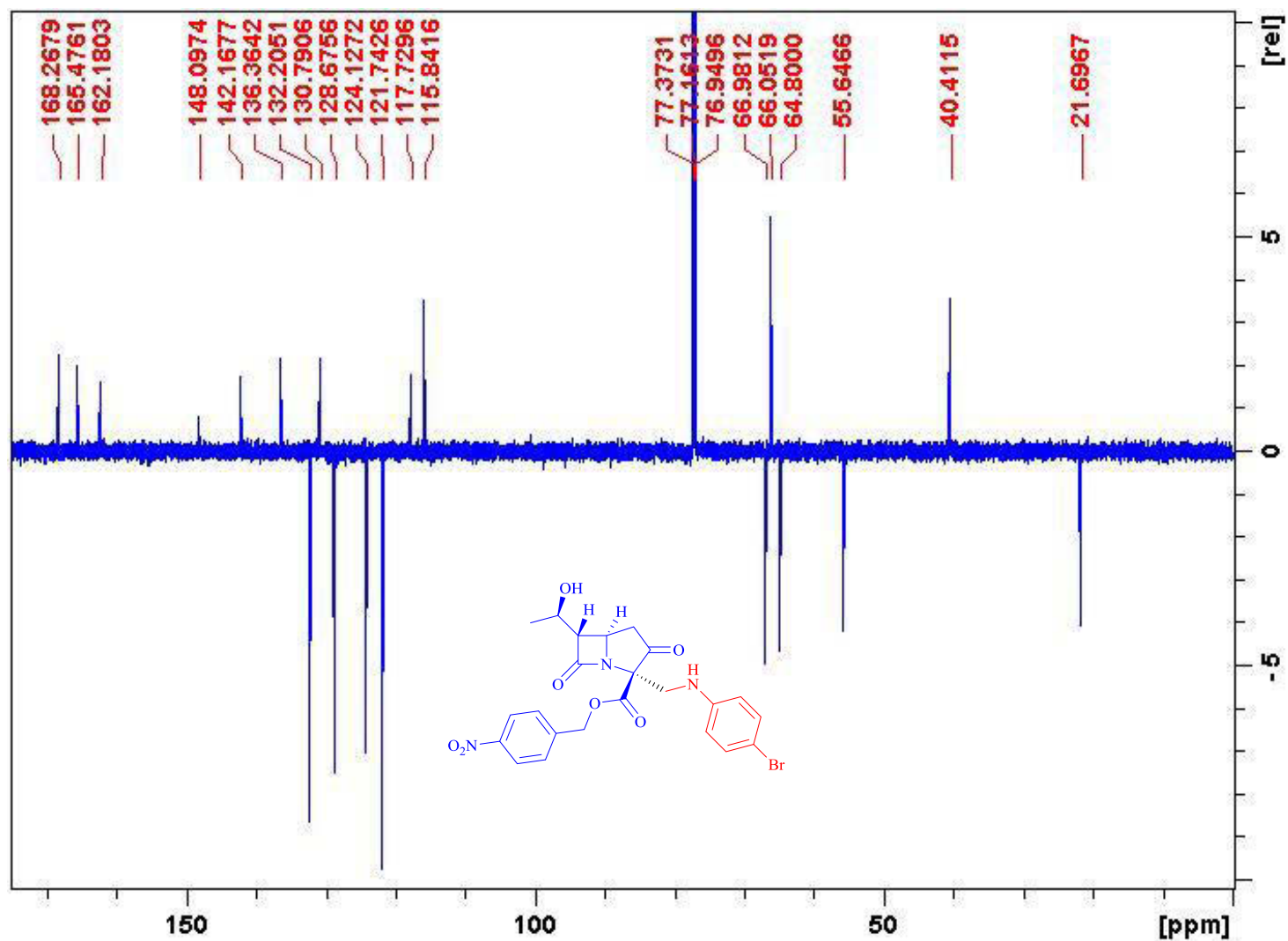
^{13}C -NMR spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((4-methoxyphenylamino)methyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (10)



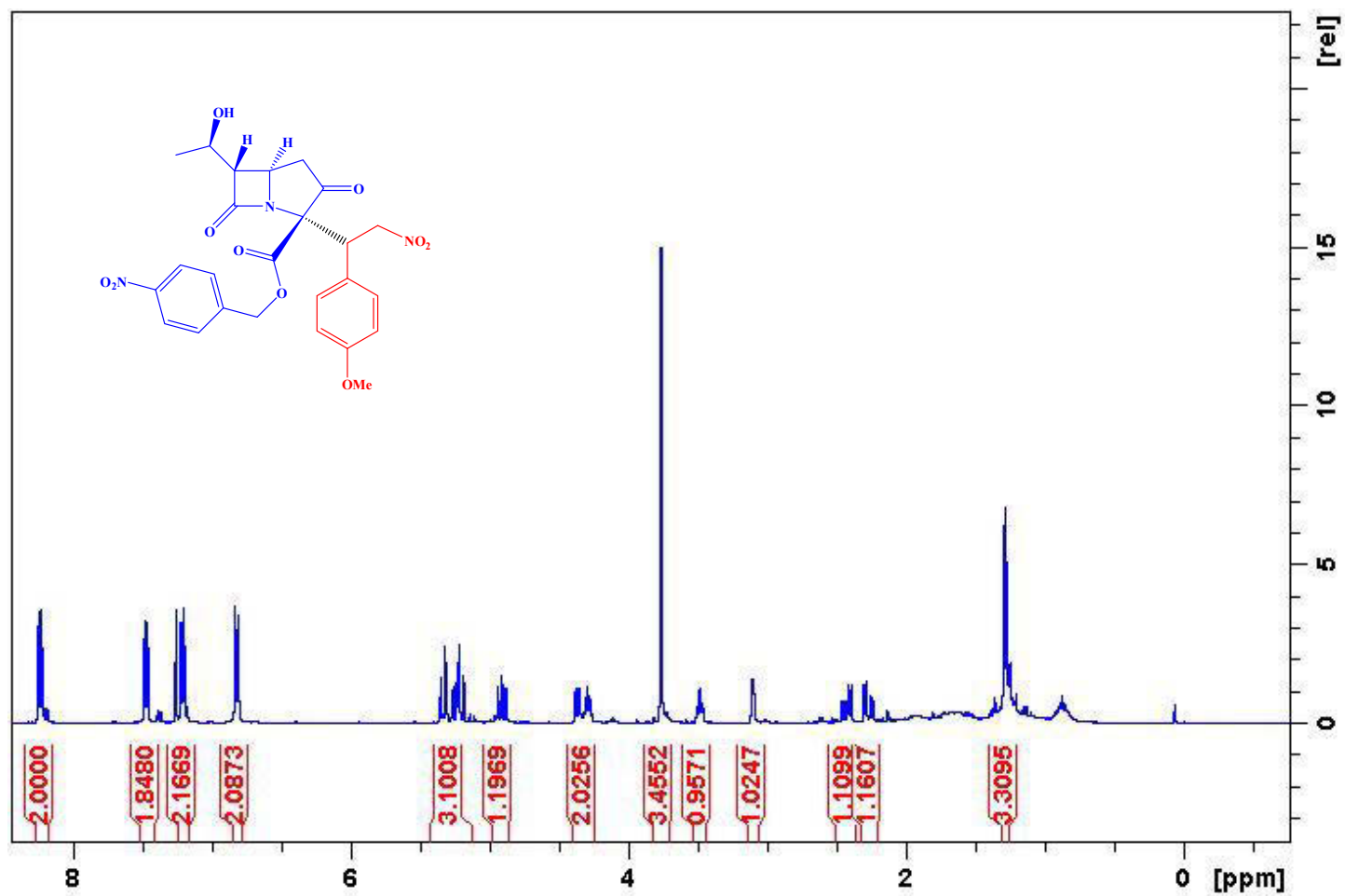
¹³C-NMR spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 2-((4-bromophenylamino)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (11)



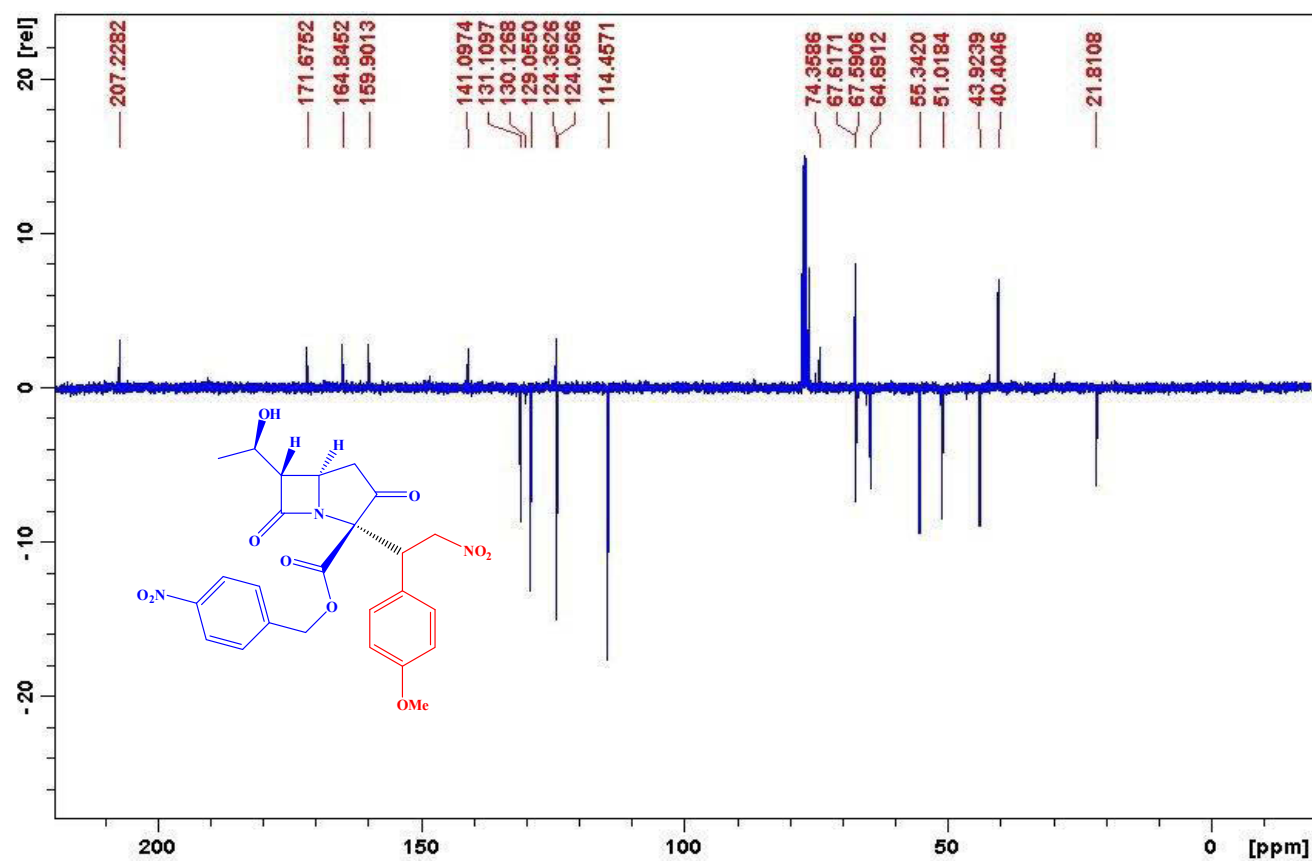
^{13}C -NMR spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 2-((4-bromophenylamino)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (11)



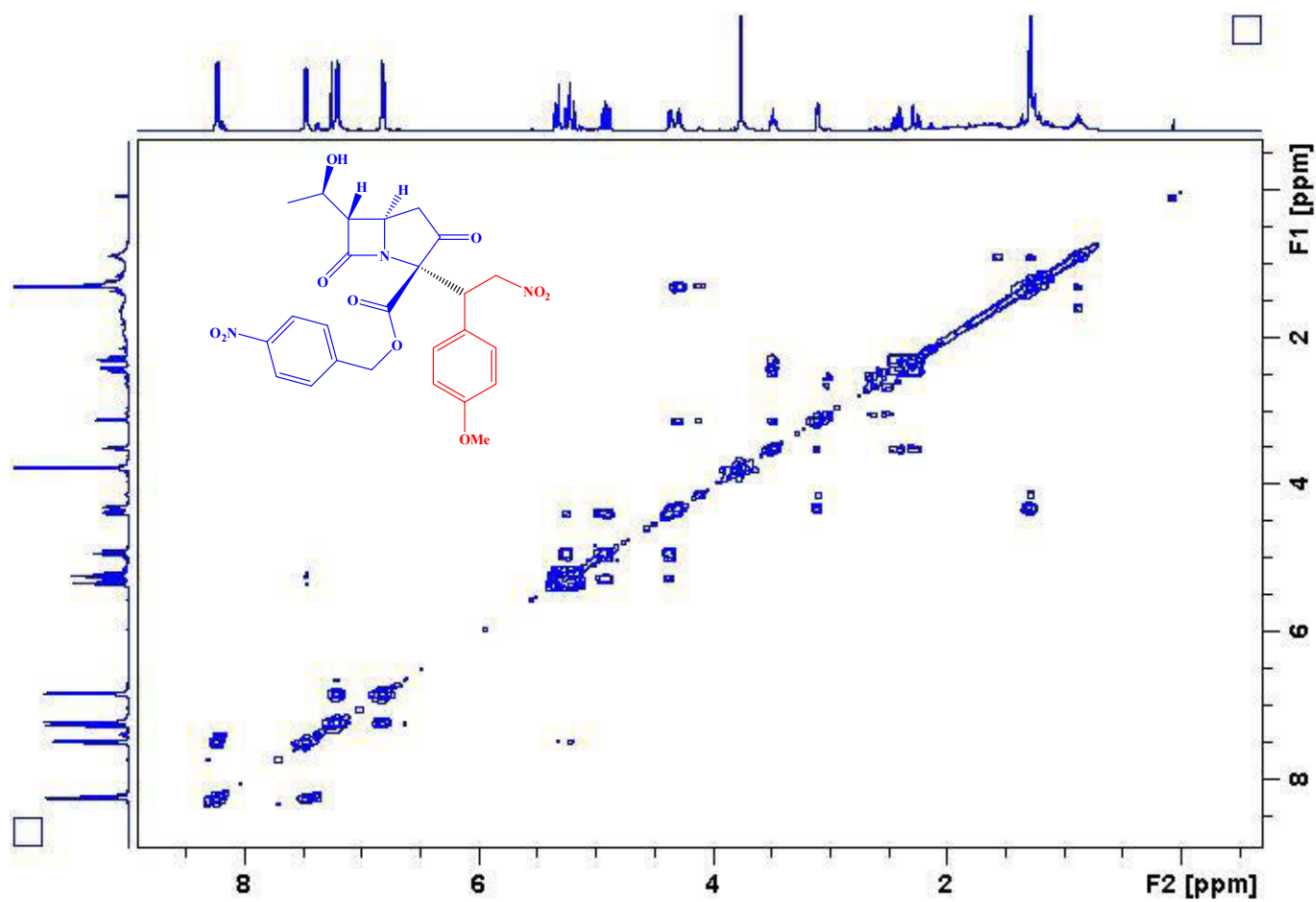
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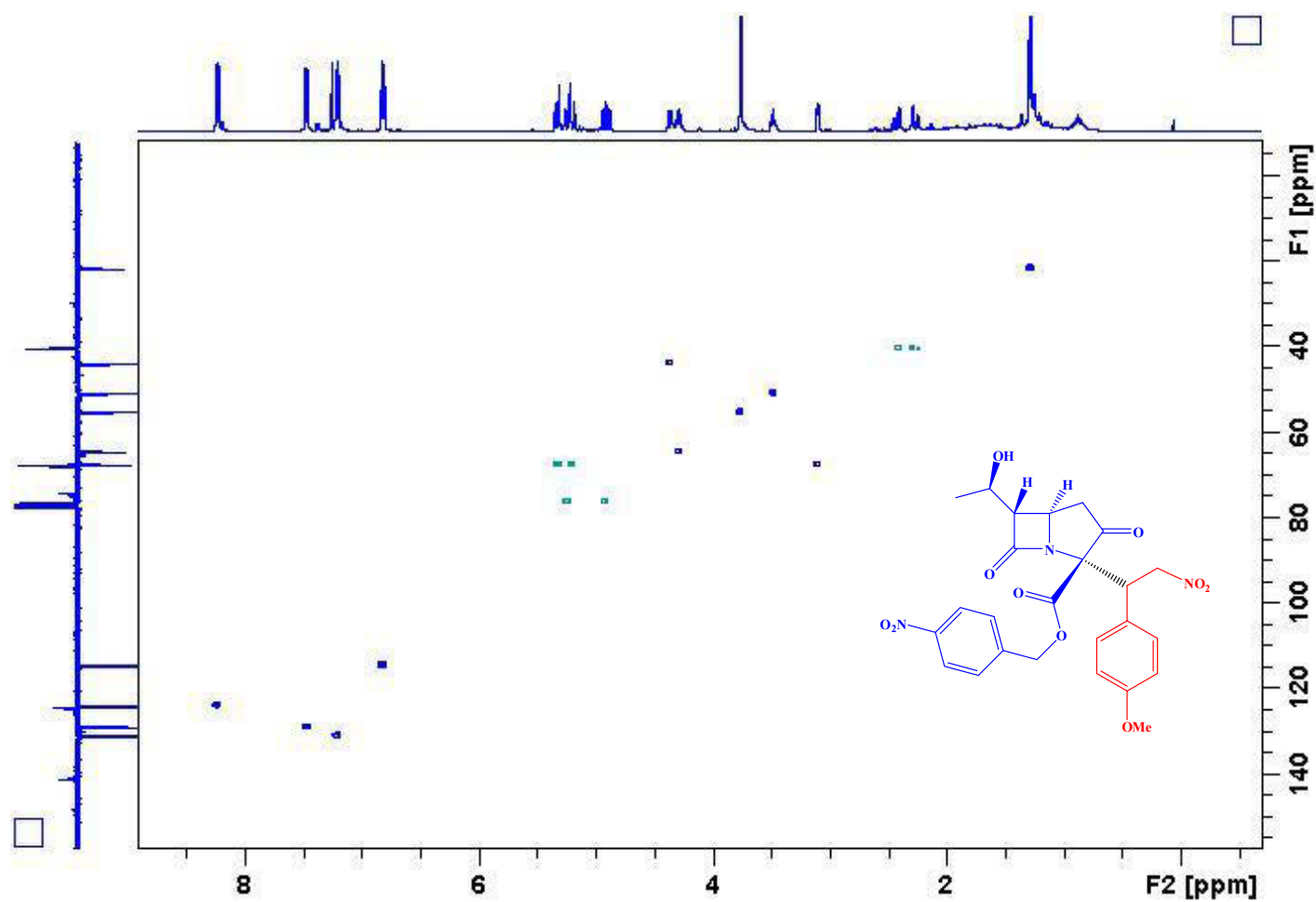
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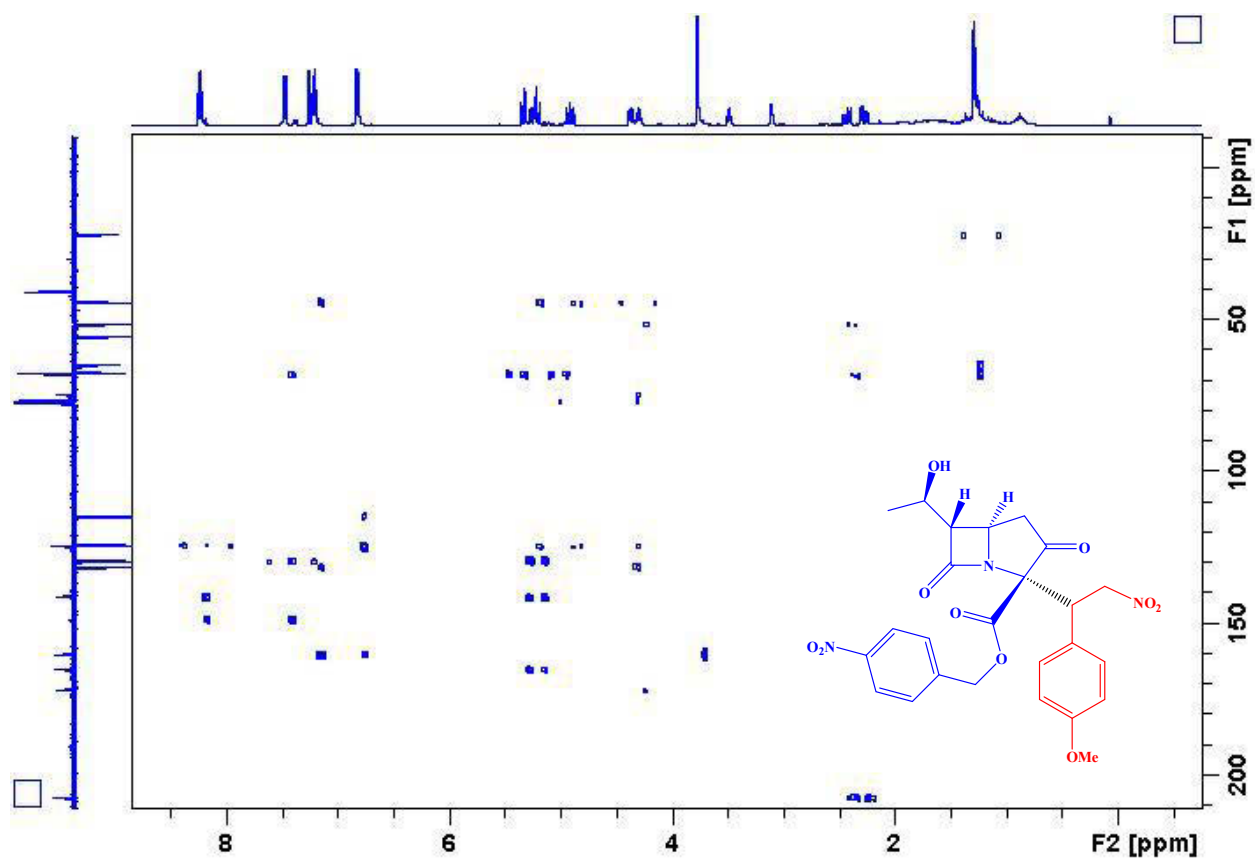
Cosy spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



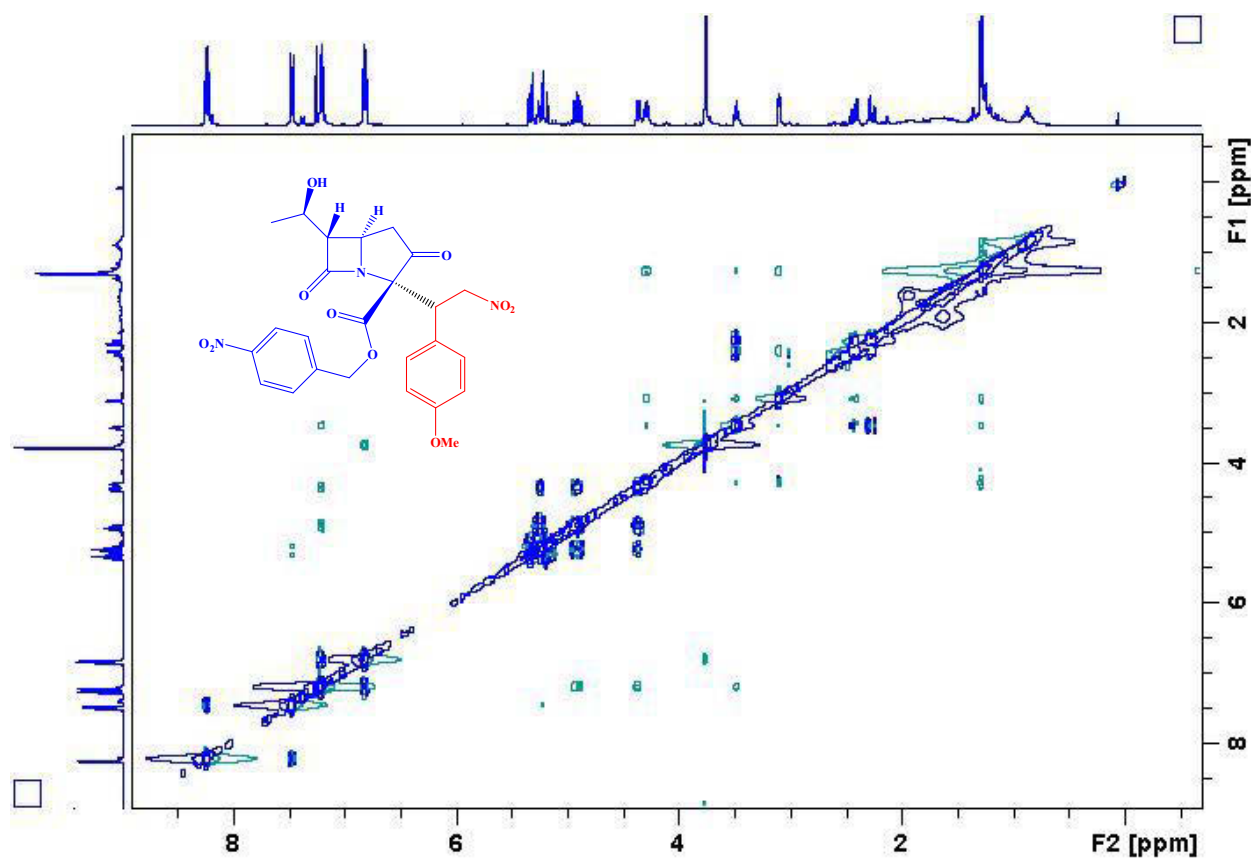
HSQC spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



HMBC spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



NOESY spectra of (2*S*,5*R*, 6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



HRMS of ((2*S*)-4-nitrobenzyl-6-((*R*)-1-hydroxyethyl)-2-(hydroxymethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate) (1)

Display Report

Analysis Info

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Method tune_mid.m
Sample Name saba377
Comment

Acquisition Date 8/30/2013 4:09:19 PM

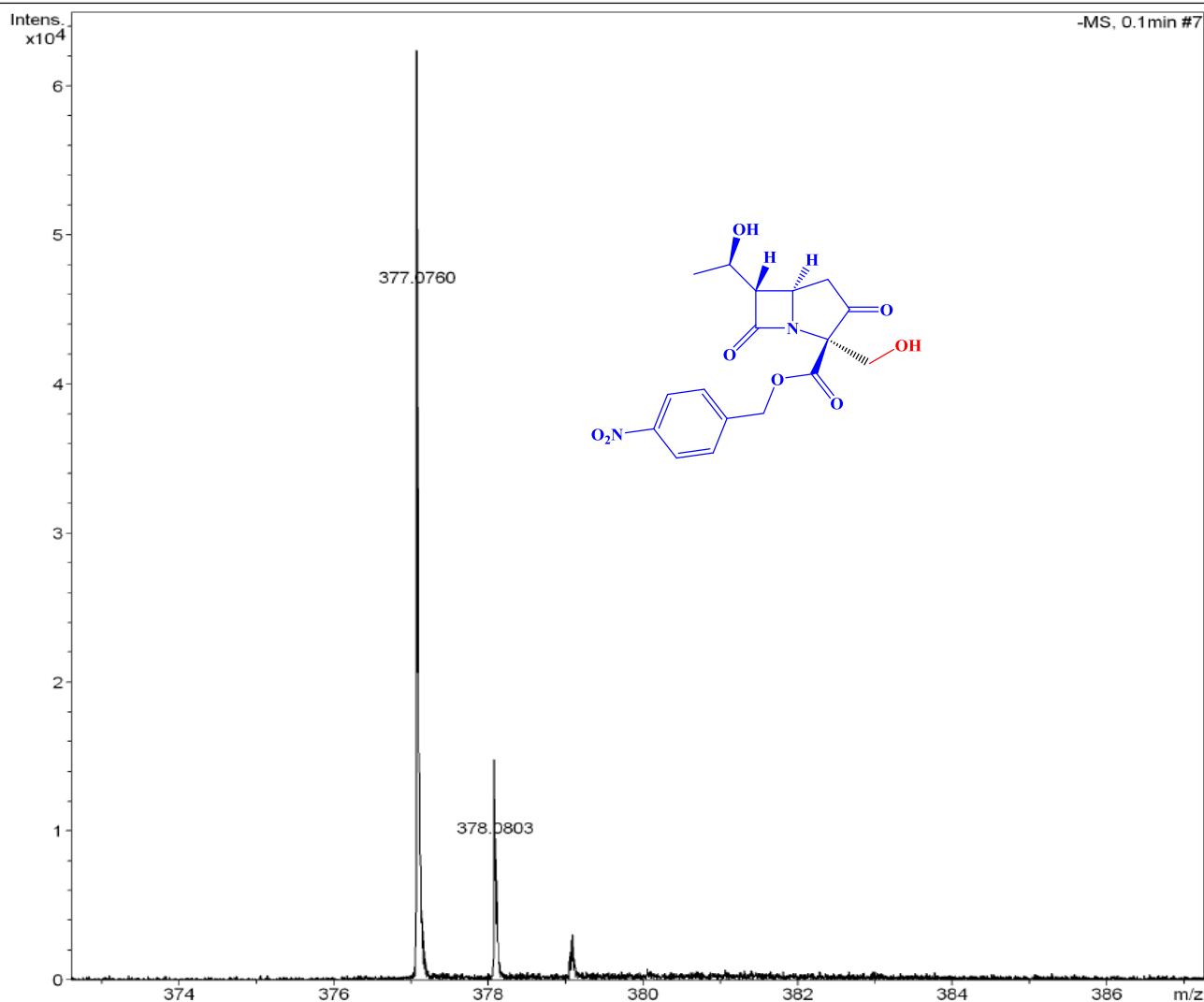
Operator BDAL@DE
Instrument maXis 21230

Acquisition Parameter

Source Type ESI
Focus Active
Scan Begin 200 m/z
Scan End 2900 m/z

Ion Polarity Negative
Set Capillary 2400 V
Set End Plate Offset -500 V
Set Collision Cell RF 2000.0 Vpp

Set Nebulizer 0.4 Bar
Set Dry Heater 180 °C
Set Dry Gas 4.0 l/min
Set Divert Valve Source



HRMS of (2S)-nitrobenzyl2-((R)-hydroxy(phenyl)methyl)-6-(1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (2)

Display Report

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Method tune_mid.m
Sample Name saba454
Comment

Acquisition Date 8/30/2013 4:18:14 PM

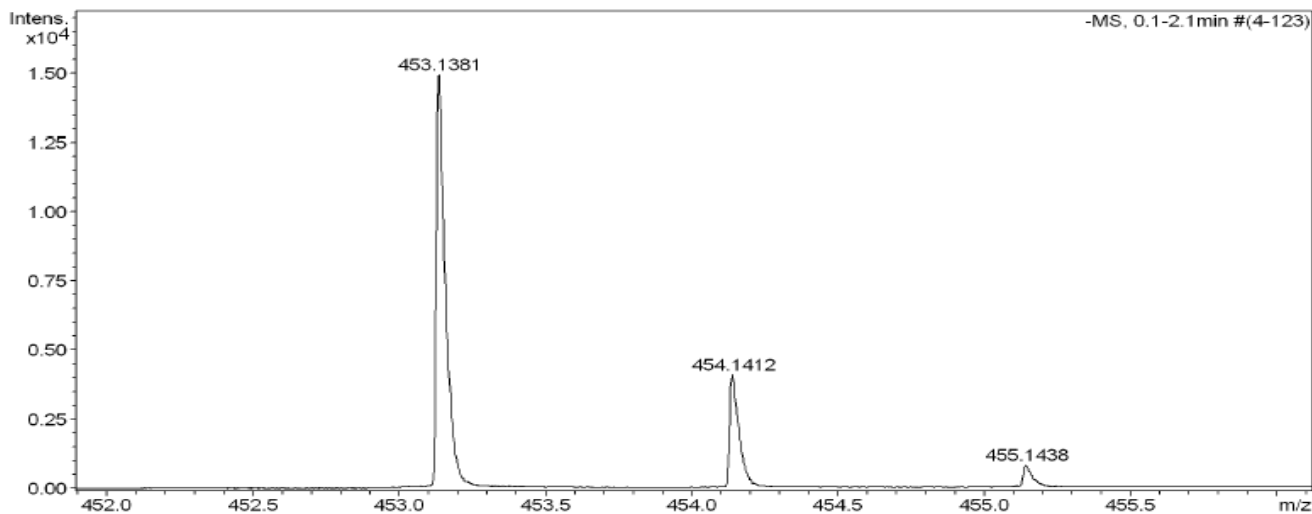
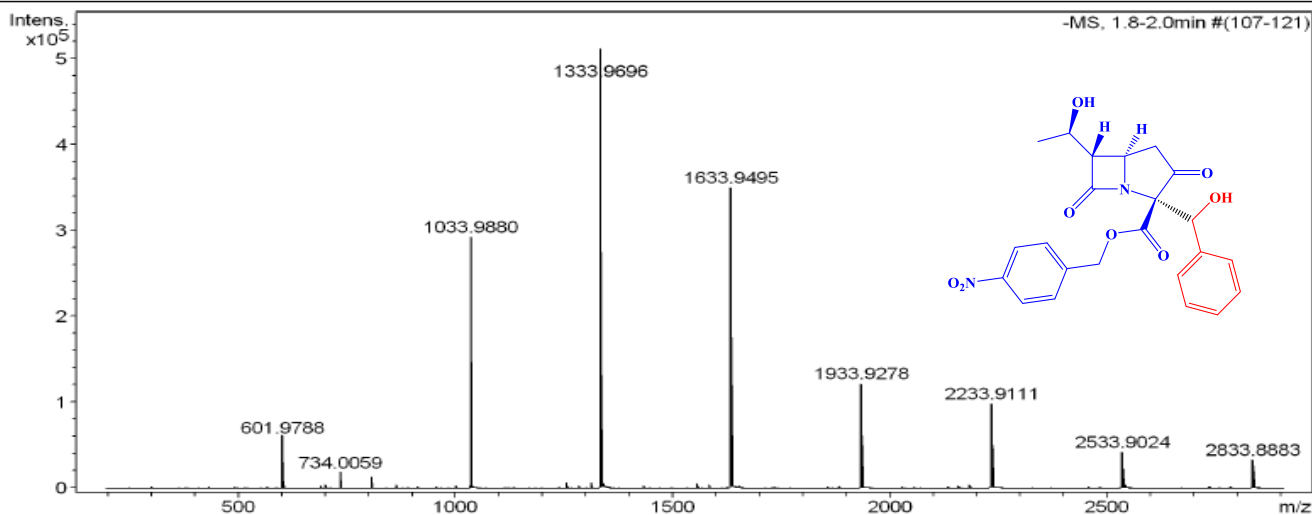
Operator BDAL@DE
Instrument maXis 21230

Acquisition Parameter

Source Type ESI
Focus Active
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Scan End 2900 m/z

Ion Polarity Negative
Set Capillary 2400 V
Set End Plate Offset -500 V
Set Collision Cell RF 2000.0 Vpp

Set Nebulizer 0.4 Bar
Set Dry Heater 180 °C
Set Dry Gas 4.0 l/min
Set Divert Valve Source



HRMS of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((phenylamino) methyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (9)

Display Report

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Comment

Acquisition Date 8/30/2013 4:27:33 PM

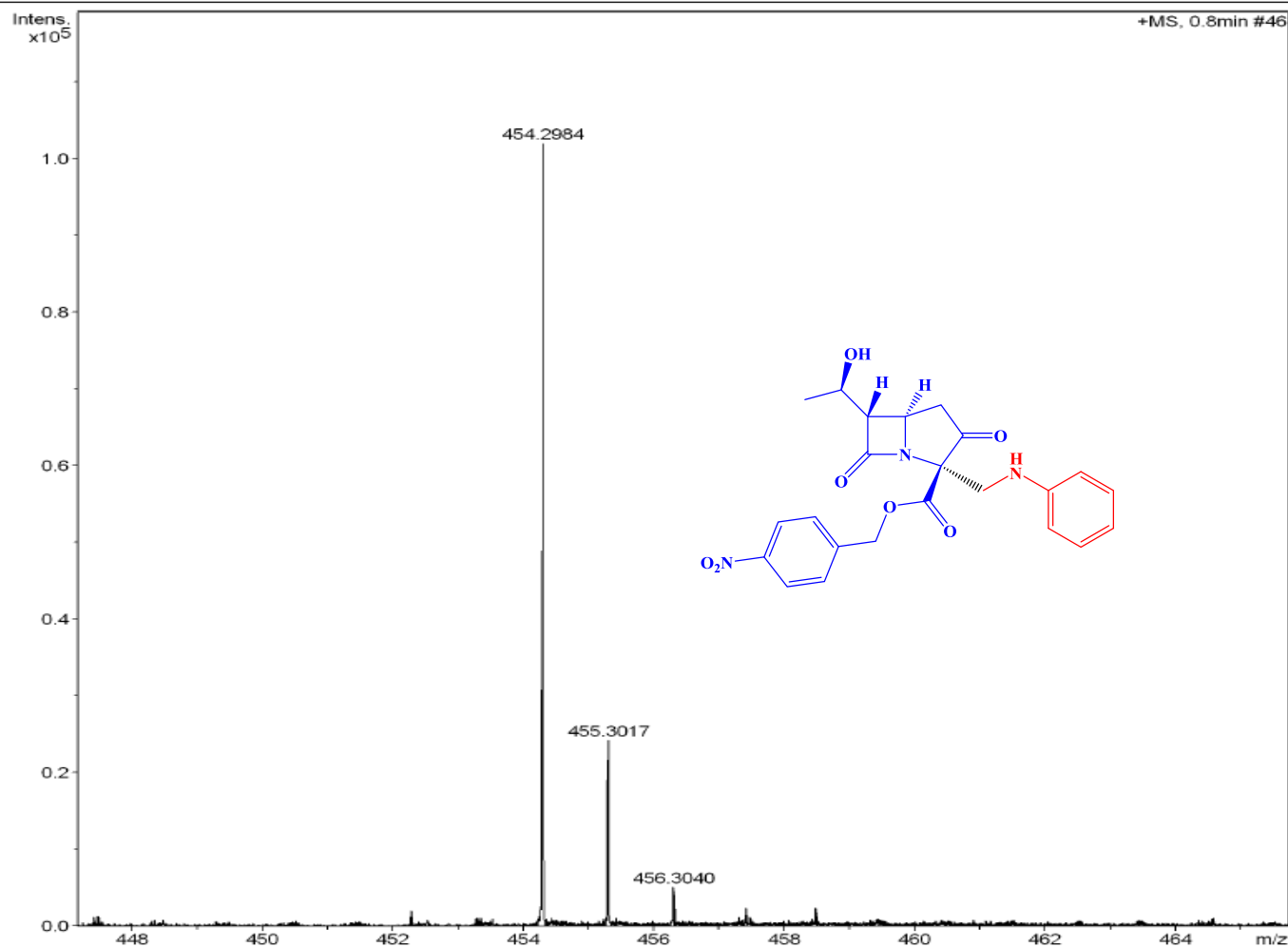
Operator BDAL@DE
Instrument maXis 21230

Acquisition Parameter

Source Type ESI
Focus Active
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Ion Polarity Positive
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Set Collision Cell RF 2000.0 Vpp

Set Nebulizer 0.4 Bar
Set Dry Heater 180 °C
Set Dry Gas 4.0 l/min
Set Divert Valve Source



HRMS of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((4-methoxyphenylamino)methyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (10)

Display Report

Analysis Info

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Method fia.m
Sample Name tunemix
Comment

Acquisition Date 10/16/2013 12:55:41 PM

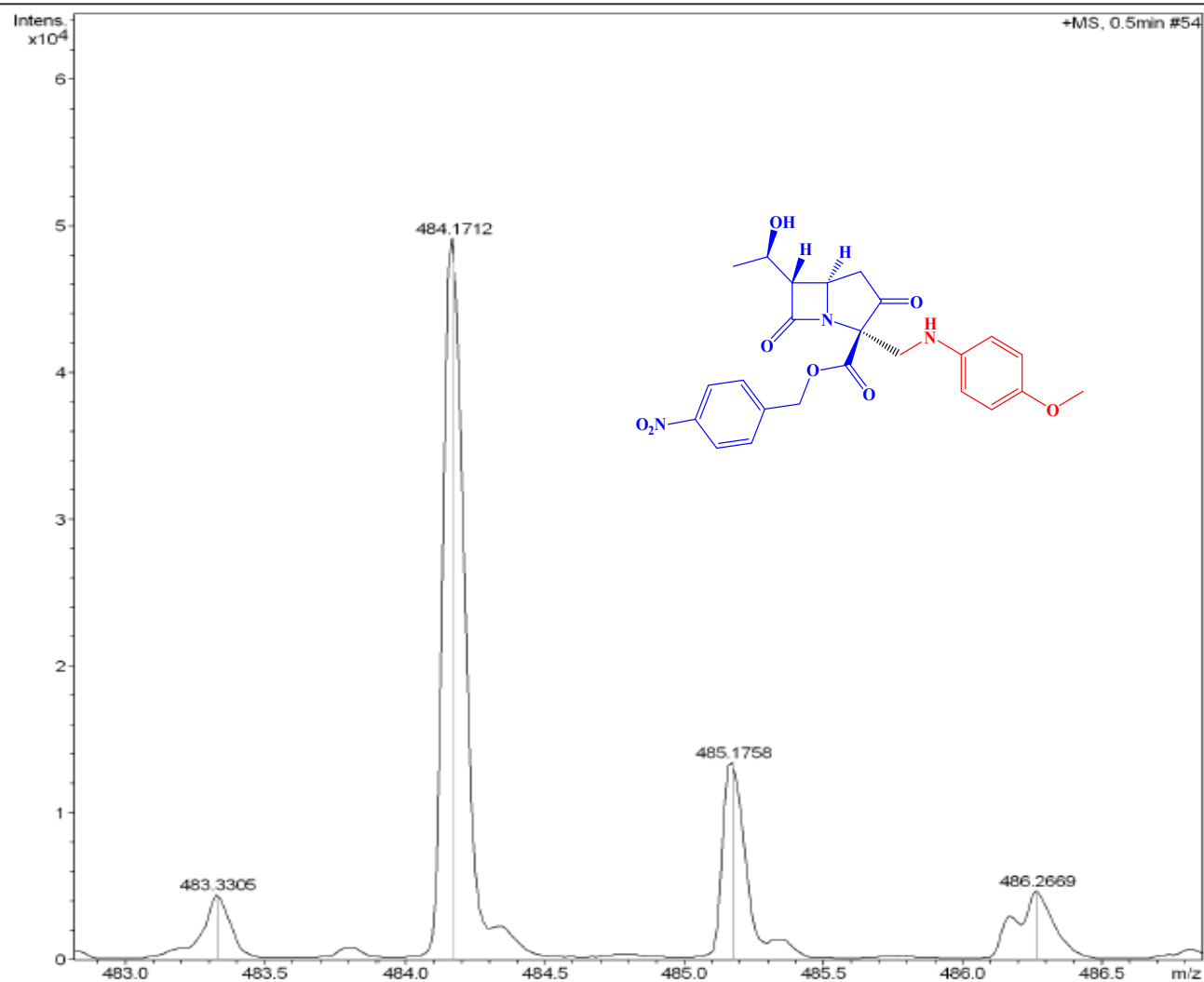
Operator BDAL@DE
Instrument micrOTOF-Q 10139

Acquisition Parameter

Source Type ESI
Focus Not active
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Scan End 3000 m/z

Ion Polarity Positive
Set Capillary 4500 V
Set End Plate Offset -500 V
Set Collision Cell RF 500.0 Vpp

Set Nebulizer 0.4 Bar
Set Dry Heater 200 °C
Set Dry Gas 4.0 l/min
Set Divert Valve Source



HRMS of (2*S*,5*R*,6*S*)-4-nitrobenzyl 2-((4-bromophenylamino)methyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (11)

Display Report

Analysis Info

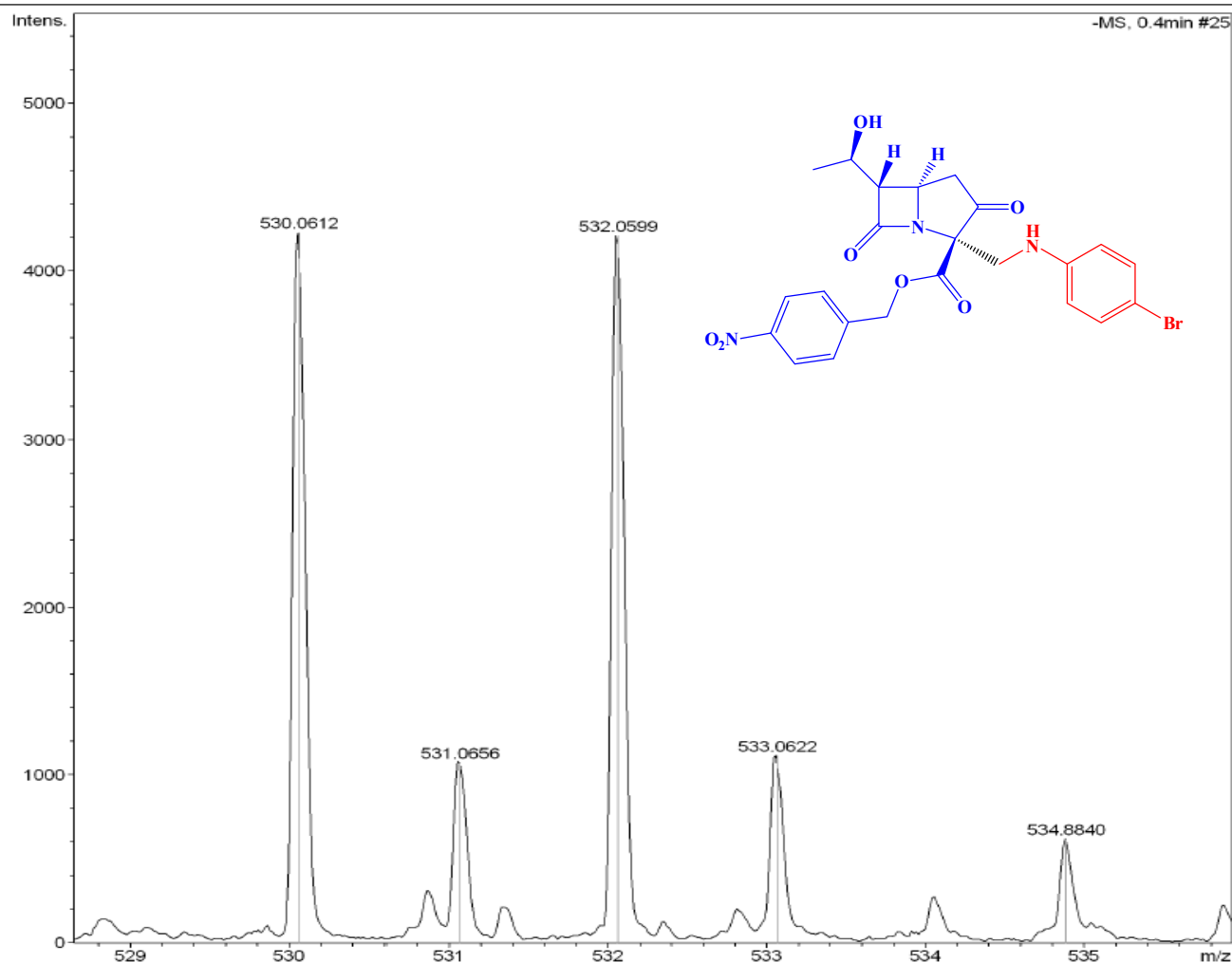
Analysis Name D:\Data\thavi\bromo.d
 Method fia_neg.m
 Sample Name tunemix
 Comment

Acquisition Date 10/16/2013 12:39:47 PM

Operator BDAL@DE
 Instrument micrOTOF-Q 10139

Acquisition Parameter

| | | | | | |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI | Ion Polarity | Negative | Set Nebulizer | 0.4 Bar |
| Focus | Not active | Set Capillary | 3500 V | Set Dry Heater | 200 °C |
| Scan Begin | 50 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 4.0 l/min |
| Scan End | 3000 m/z | Set Collision Cell RF | 500.0 Vpp | Set Divert Valve | Source |



HRMS of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxy phenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (12)

Display Report

Analysis Info

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Method tune_mid.m
Sample Name st527
Comment

Acquisition Date 8/30/2013 3:17:00 PM

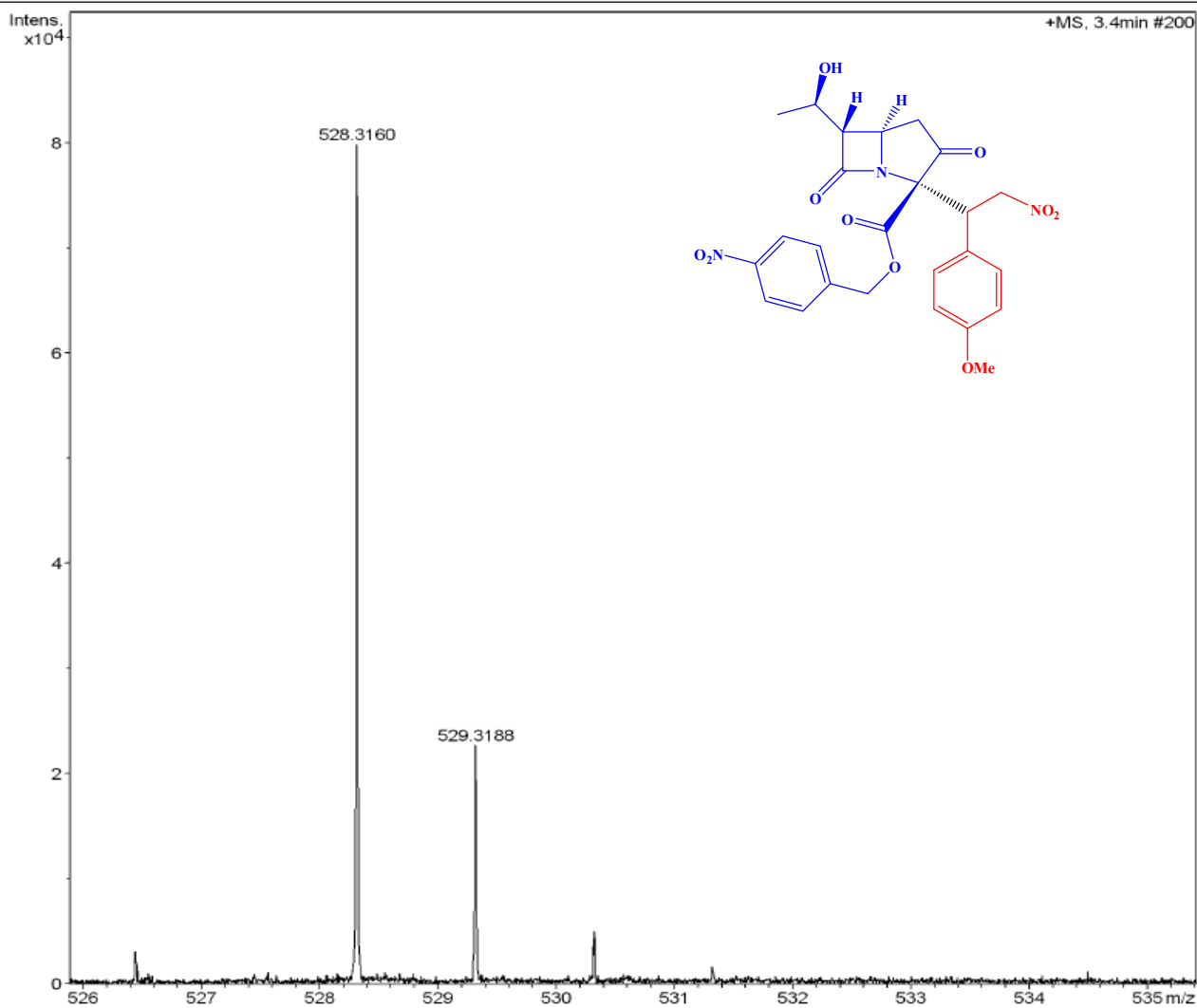
Operator BDAL@DE
Instrument maXis 21230

Acquisition Parameter

Source Type ESI
Focus Active
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Scan End 2900 m/z

Ion Polarity Positive
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Set End Plate Offset -500 V
Set Collision Cell RF 2000.0 Vpp

Set Nebulizer 0.4 Bar
Set Dry Heater 180 °C
Set Dry Gas 4.0 l/min
Set Divert Valve Source



HRMS of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxoclopentyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (13)

Display Report

Analysis Info

Analysis Name D:\Data\sibusiso\430000001.d
Method tune_mid.m
Sample Name 430
Comment

Acquisition Date 8/30/2013 4:23:05 PM

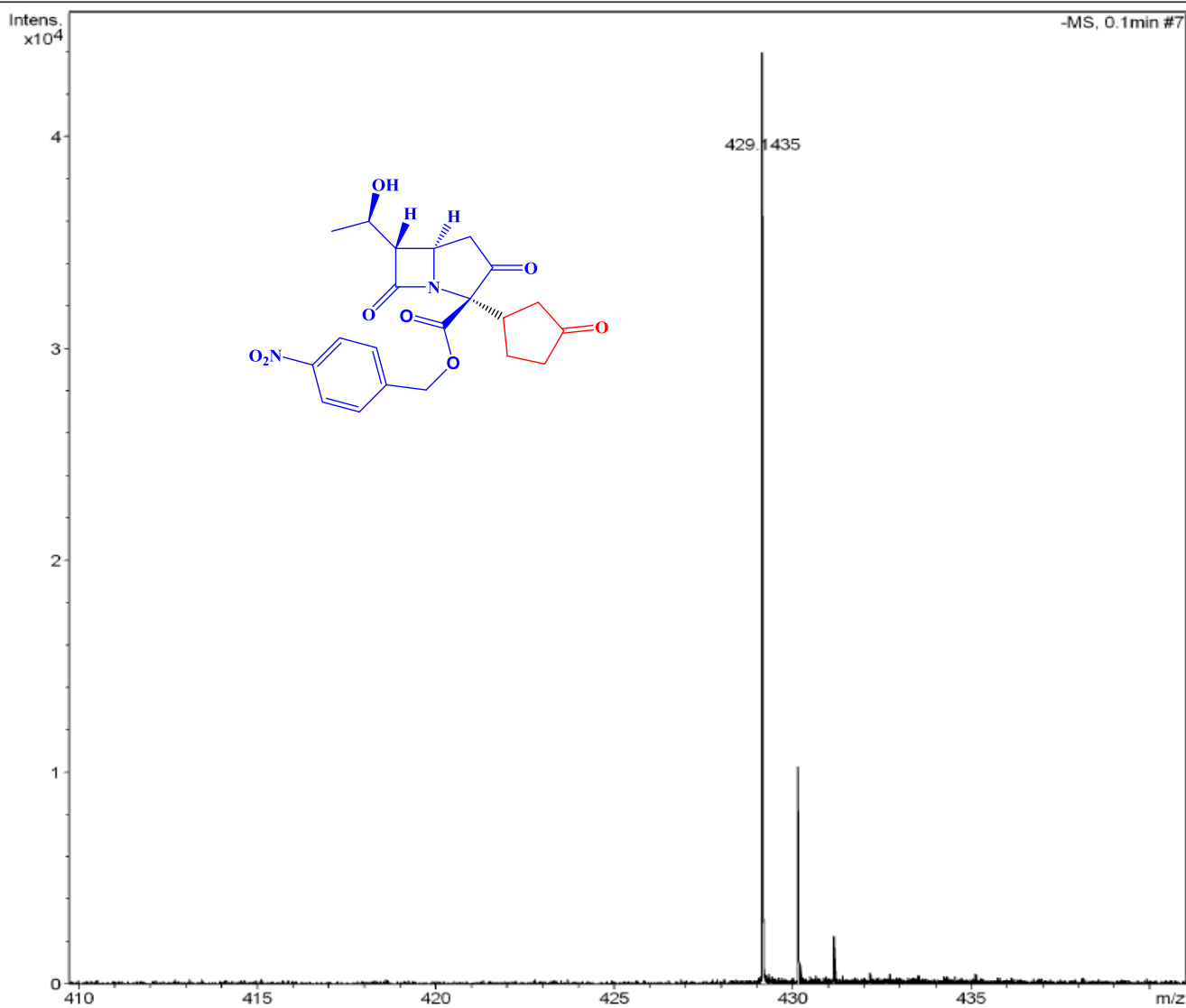
Operator BDAL@DE
Instrument maXis 21230

Acquisition Parameter

Source Type ESI
Focus Active
Scan Begin 200 m/z
Scan End 2900 m/z

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Set Capillary 2400 V
Set End Plate Offset -500 V
Set Collision Cell RF 2000.0 Vpp

Set Nebulizer 0.4 Bar
Set Dry Heater 180 °C
Set Dry Gas 4.0 l/min
Set Divert Valve Source



SUPPORTING INFORMATION FOR CHAPTER 3

UNIVERSITY OF KWAZULU-NATAL

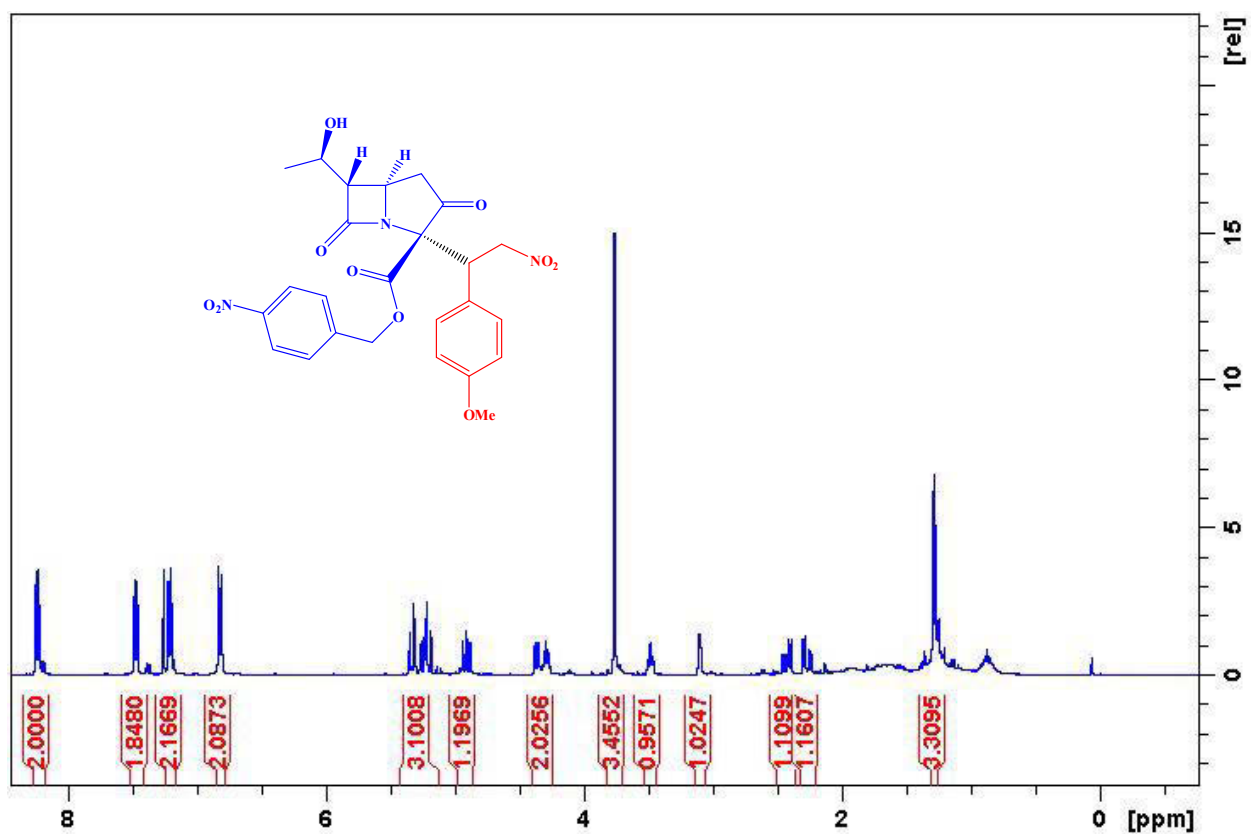
**ORGANOCATALYZED SYNTHESIS OF
CARBAPENEM β -LACTAM CORES AND
MONOBACTAM**

2014

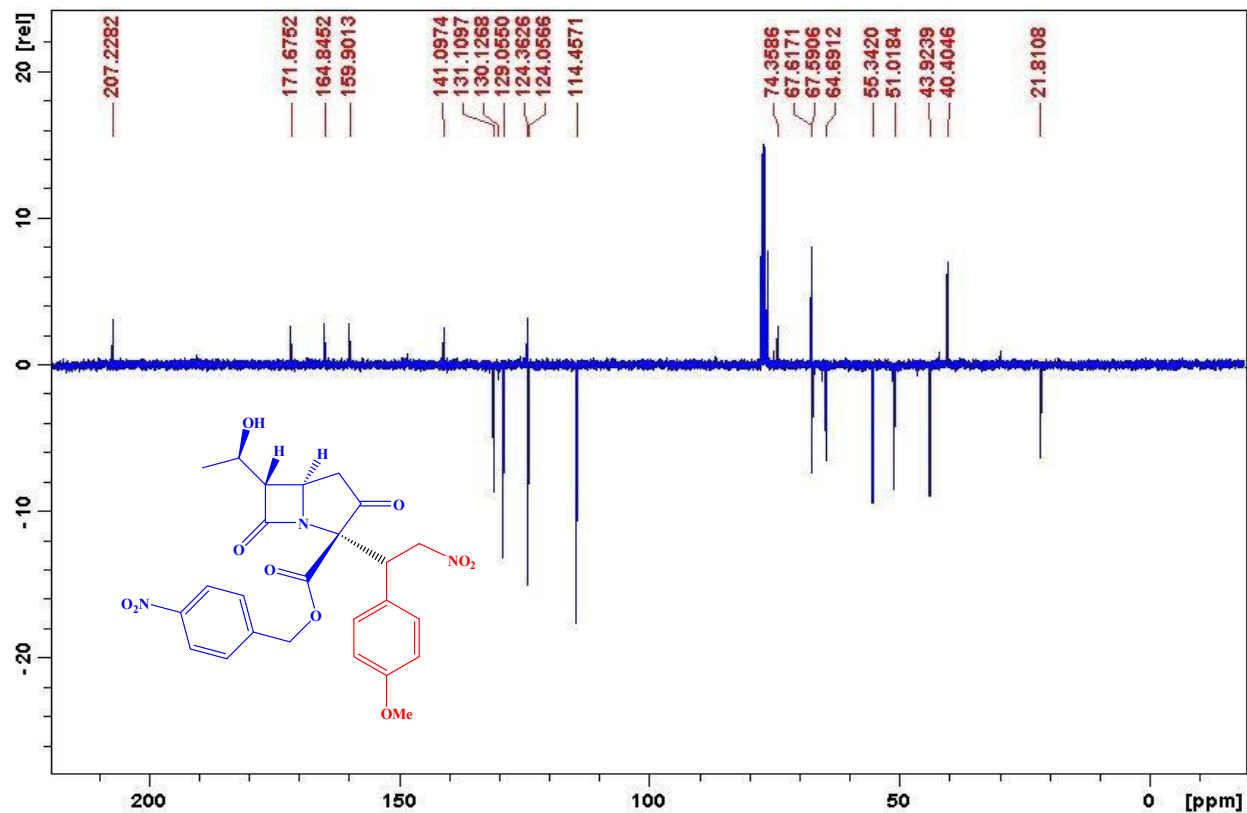
Contents:

| | |
|---|-----------|
| 1. ^1H, ^{13}C NMR and HRMS spectra..... | 95 |
|---|-----------|

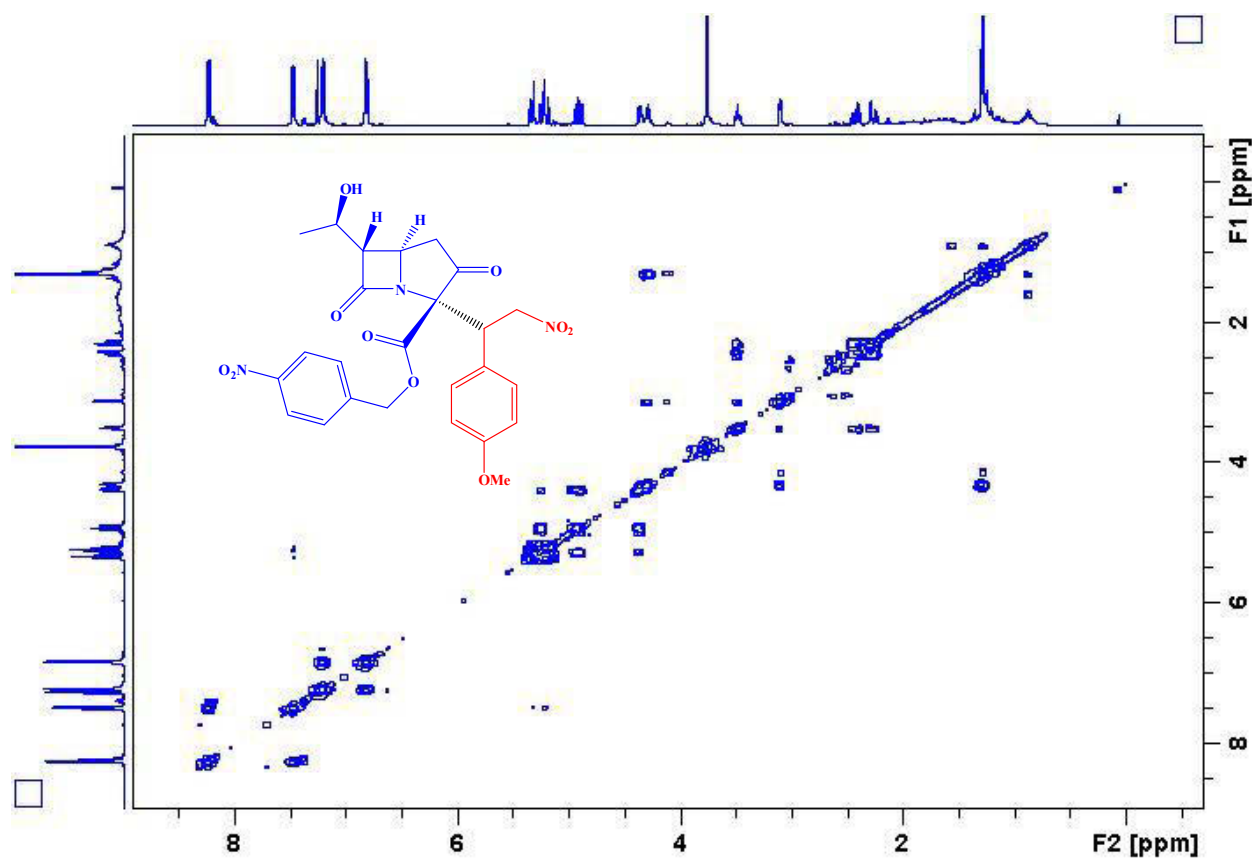
¹H-NMR spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



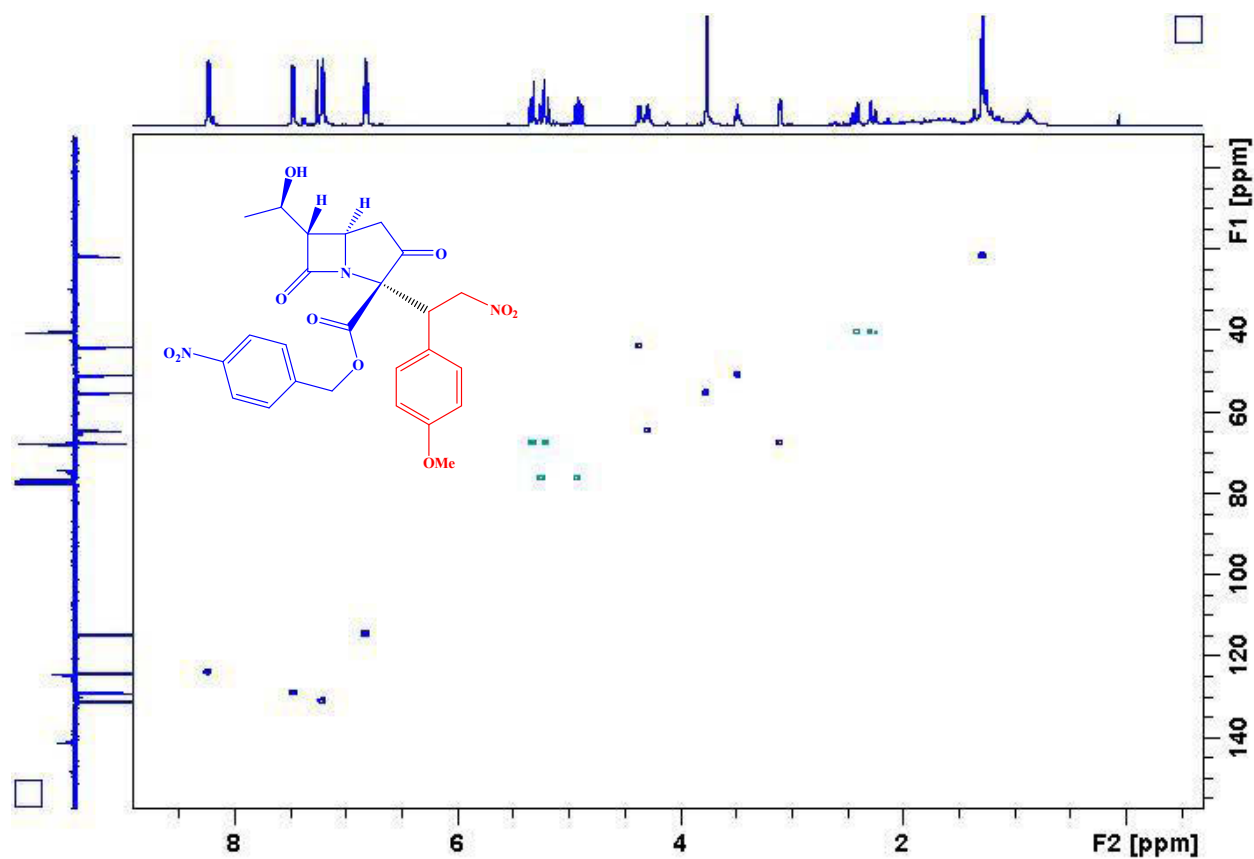
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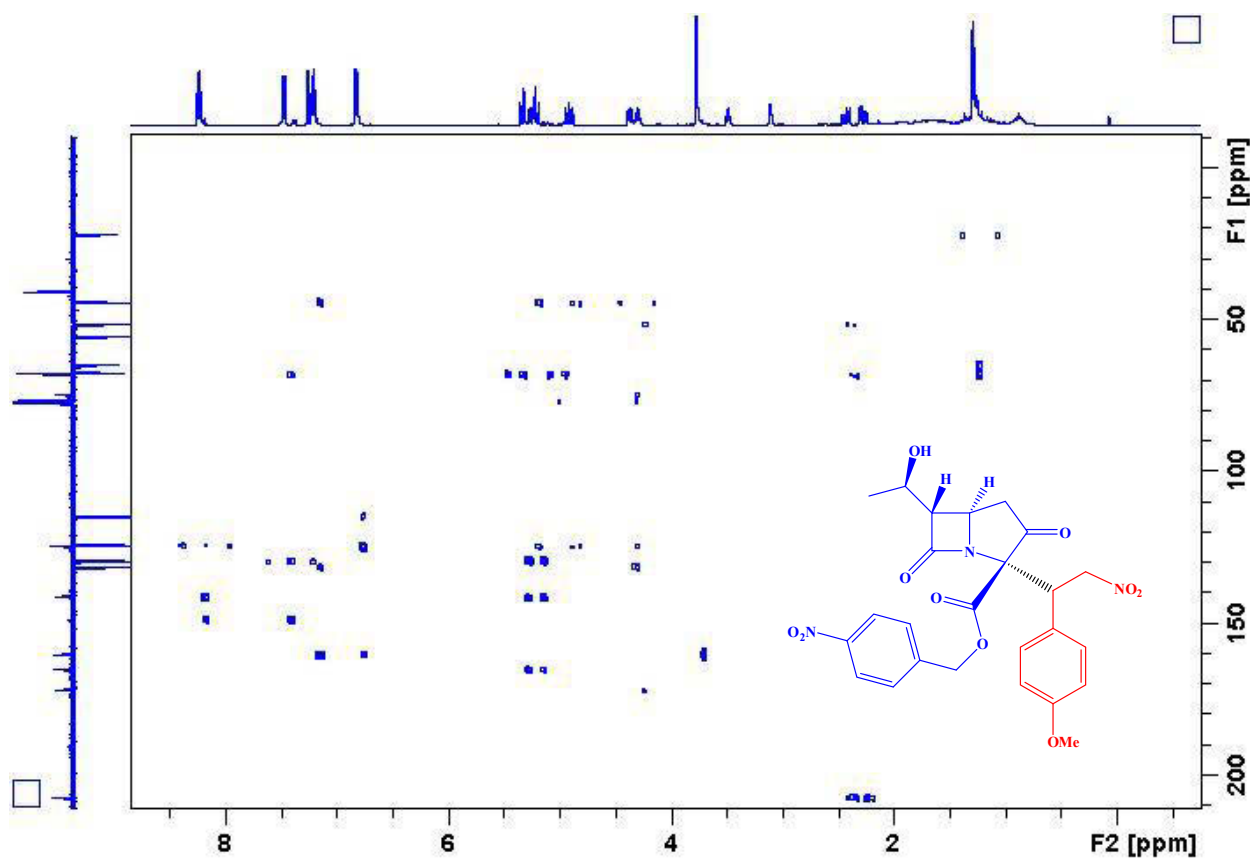
Cosy spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



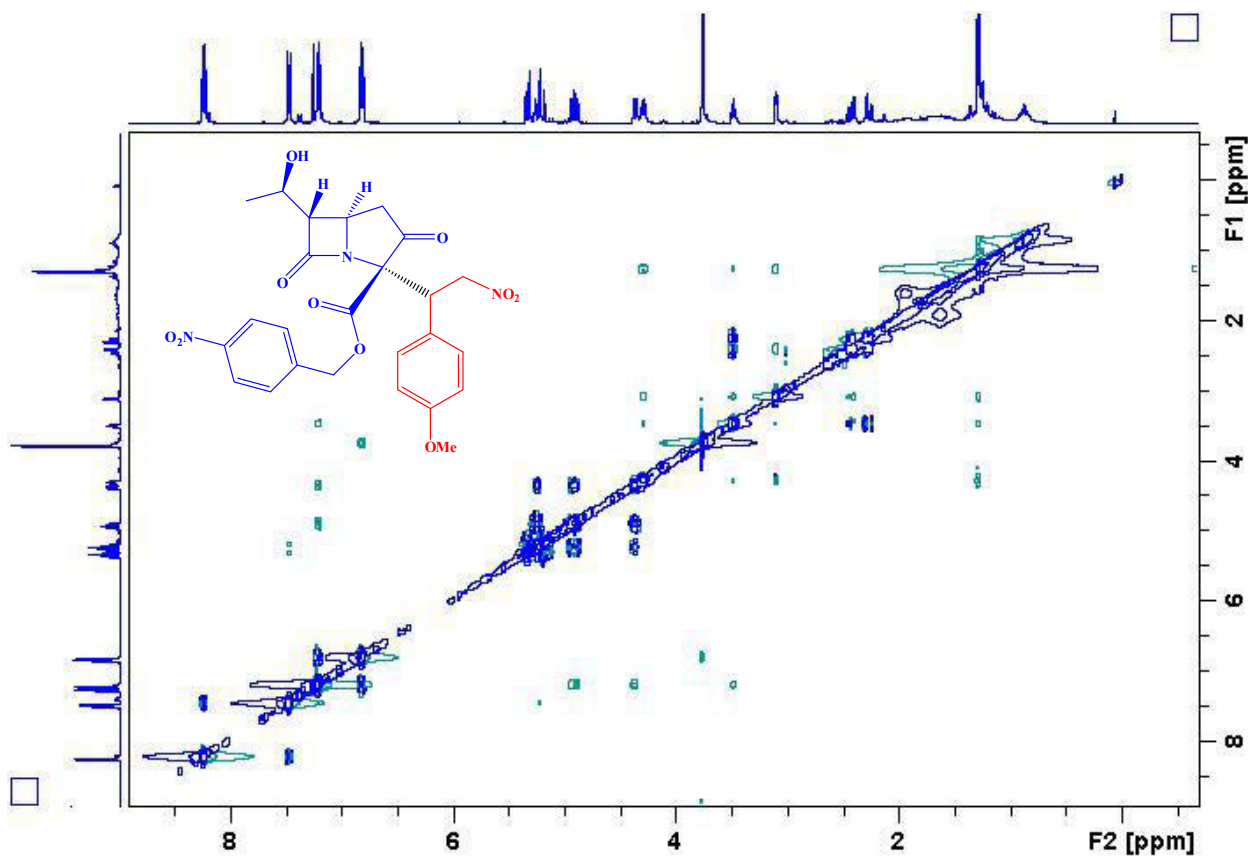
HSQC spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



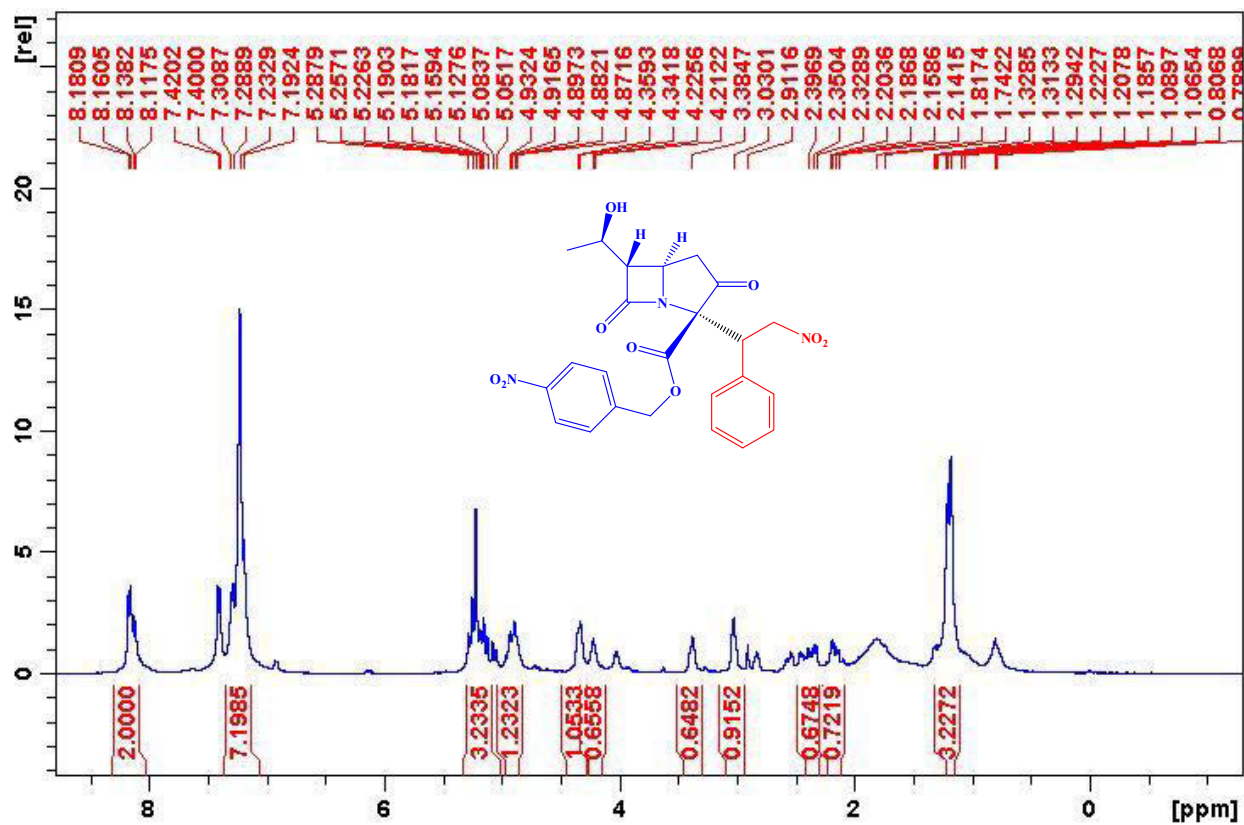
HMBC spectra of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



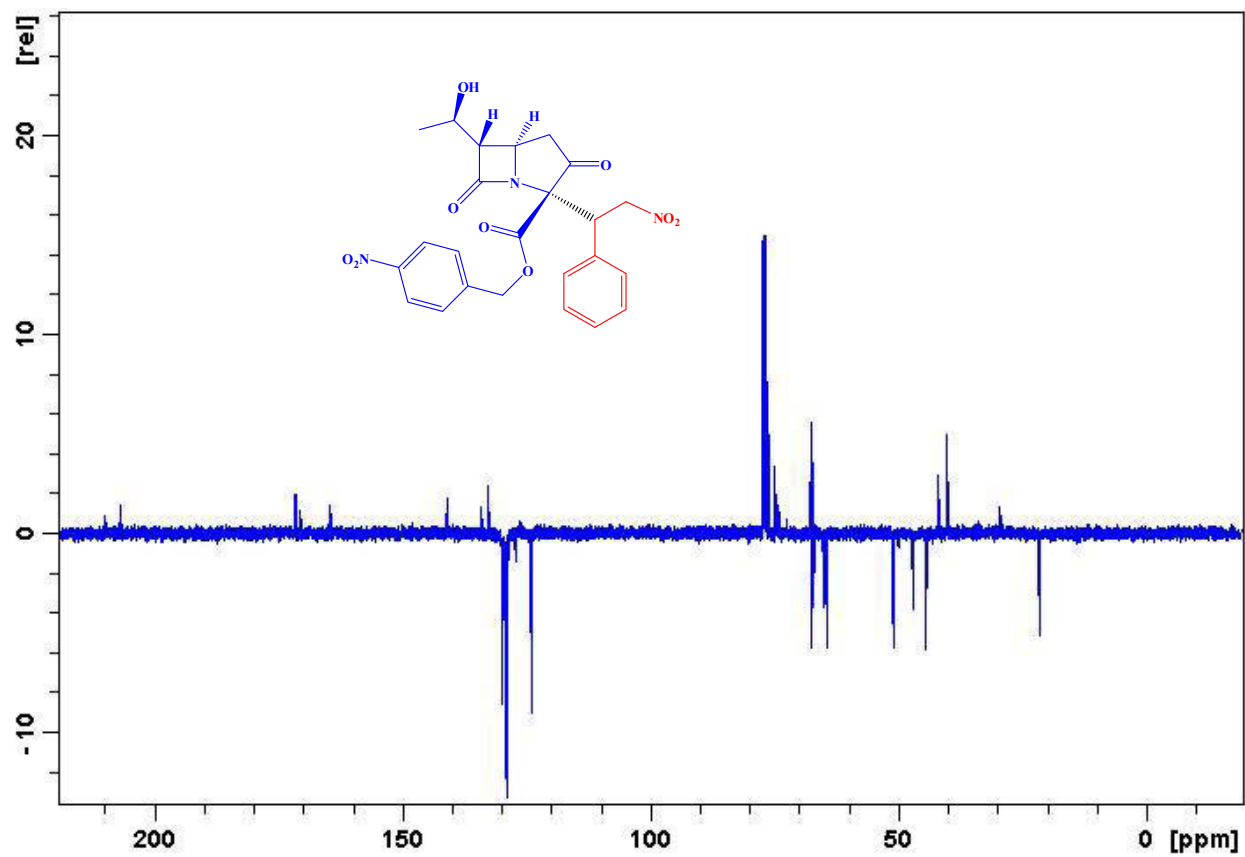
NOESY spectra of (2*S*,5*R*, 6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)



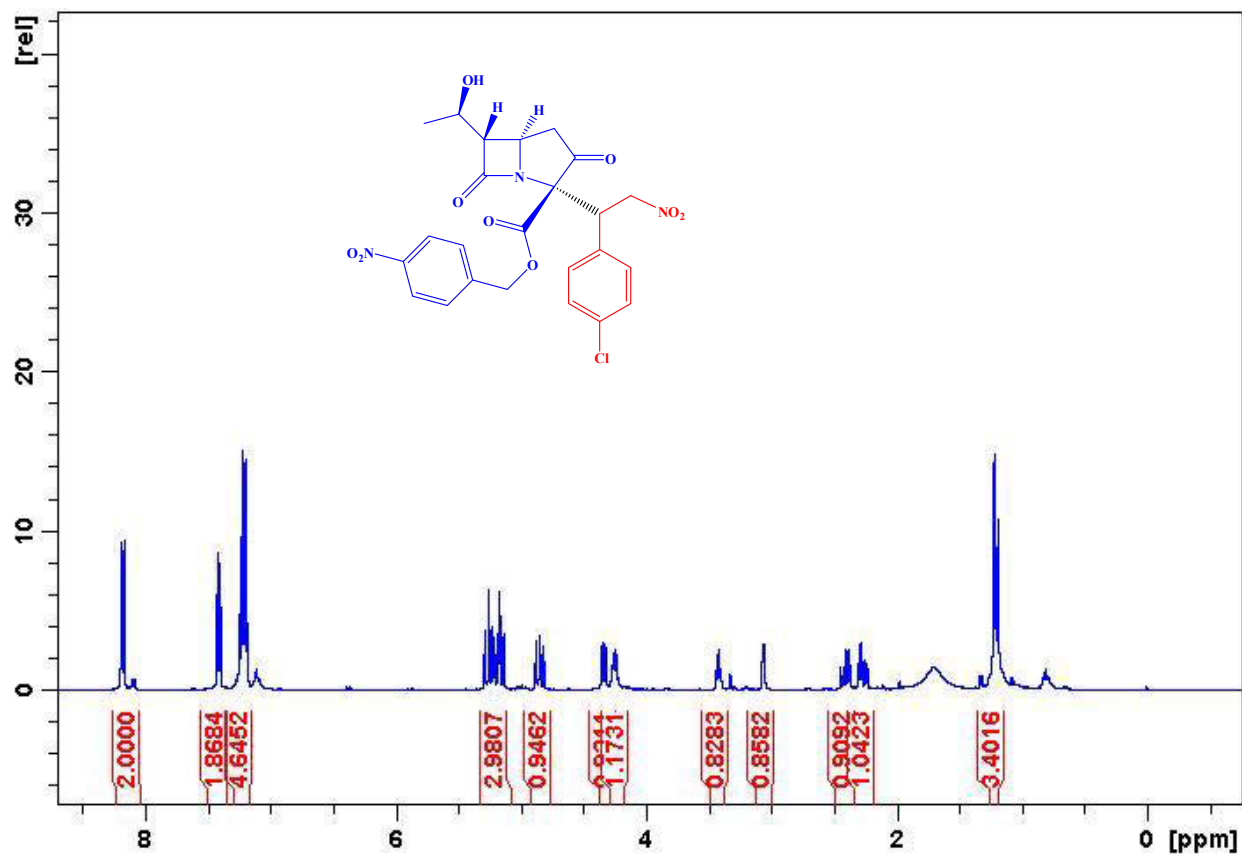
¹H NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*R*)-2-nitro-1-phenylethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3b)



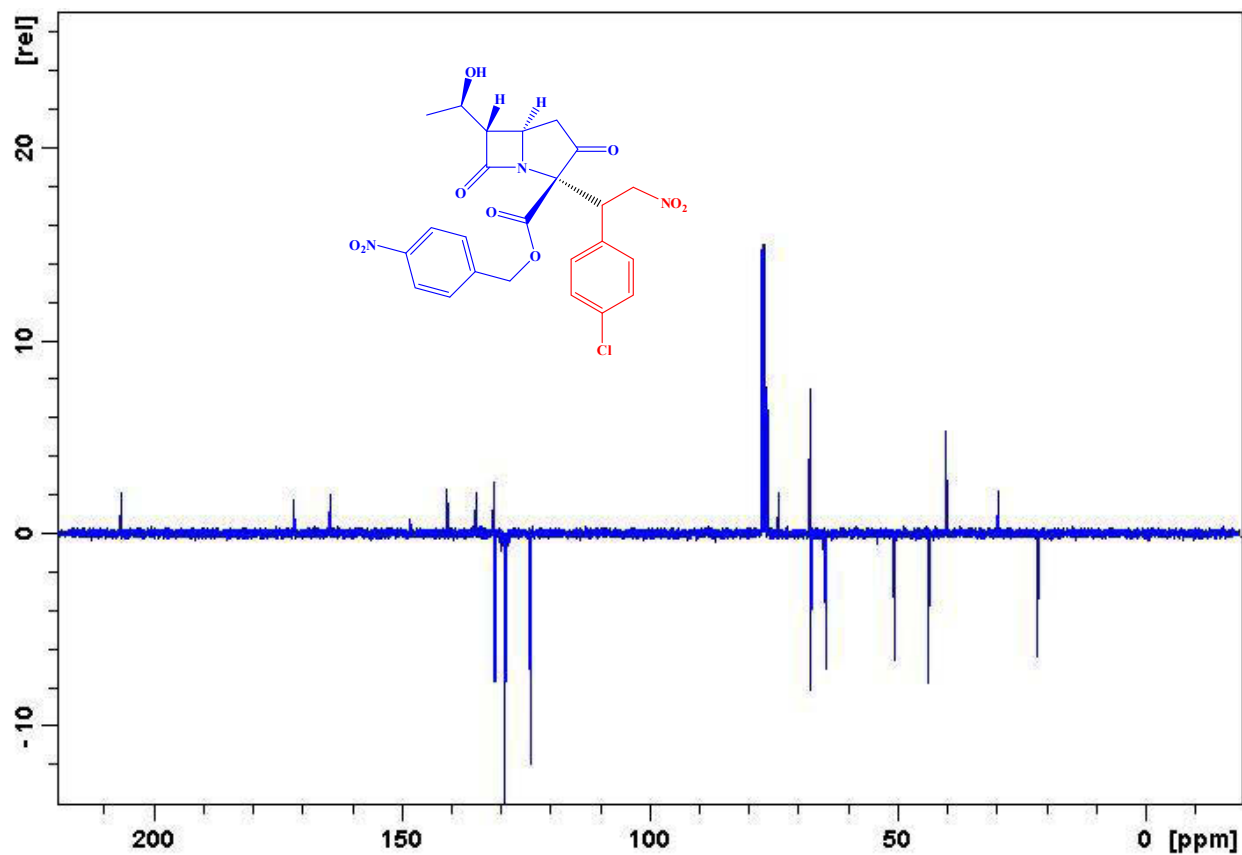
¹³C NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*R*)-2-nitro-1-phenylethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3b)



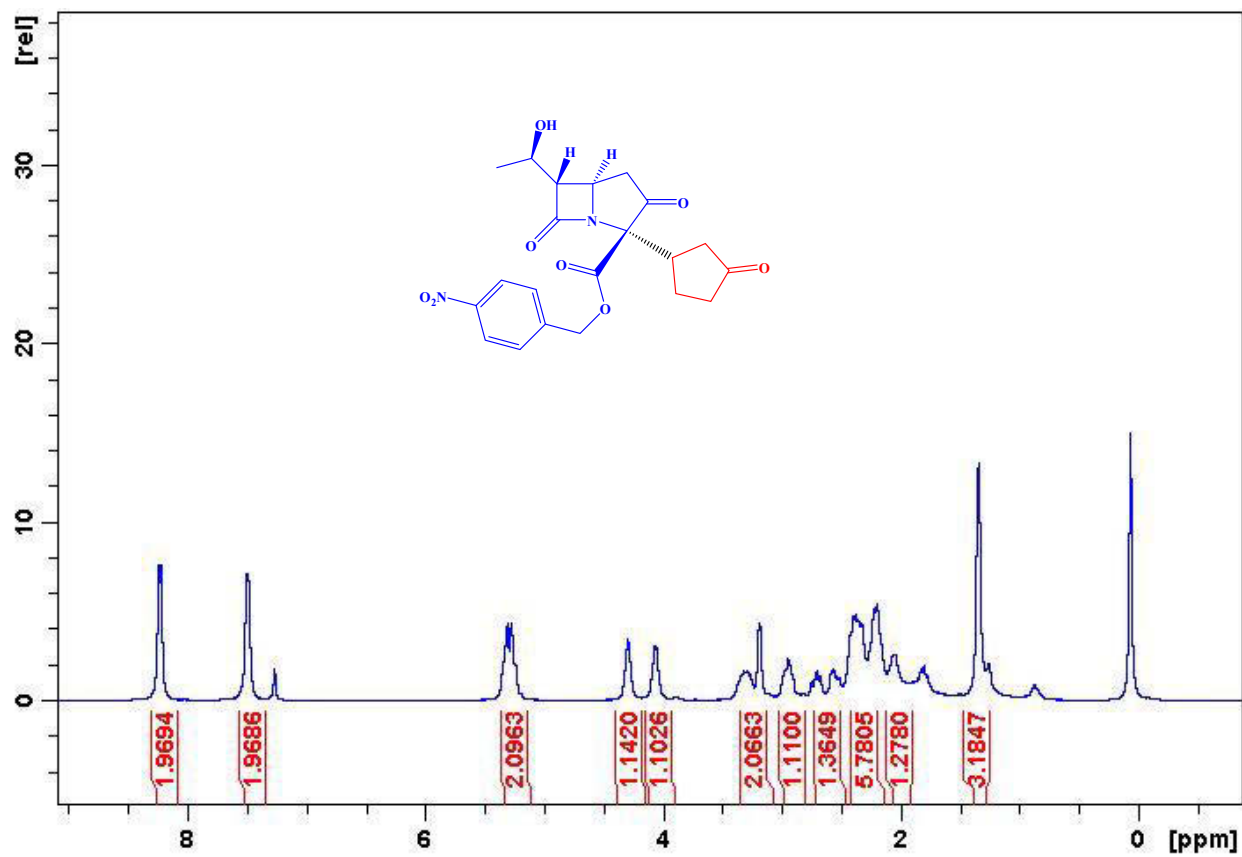
¹H NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*R*)-1-(4-chlorophenyl)-2-nitroethyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3c)



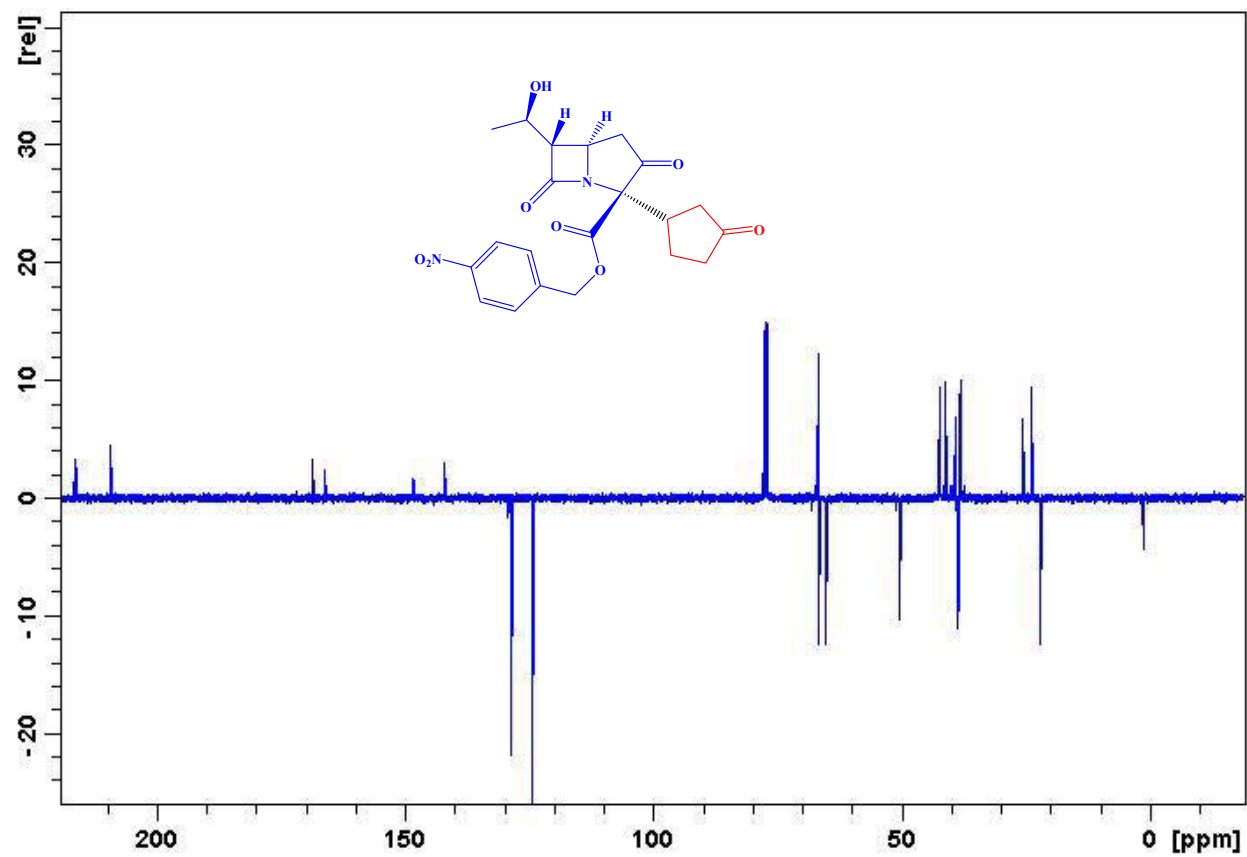
¹³C NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*R*)-1-(4-chlorophenyl)-2-nitroethyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3c)



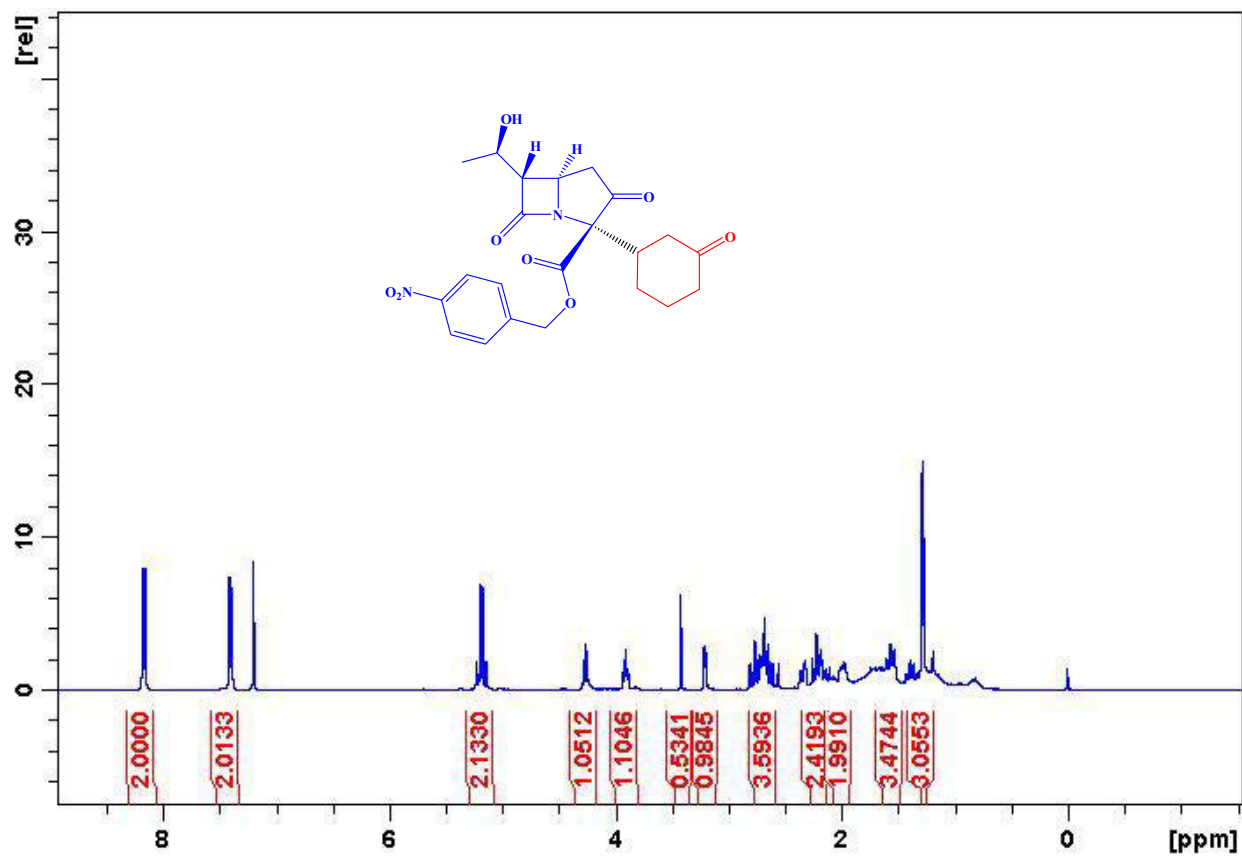
¹H NMR spectra of (2*S*, 5*R*, 6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxocyclopentyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5a)



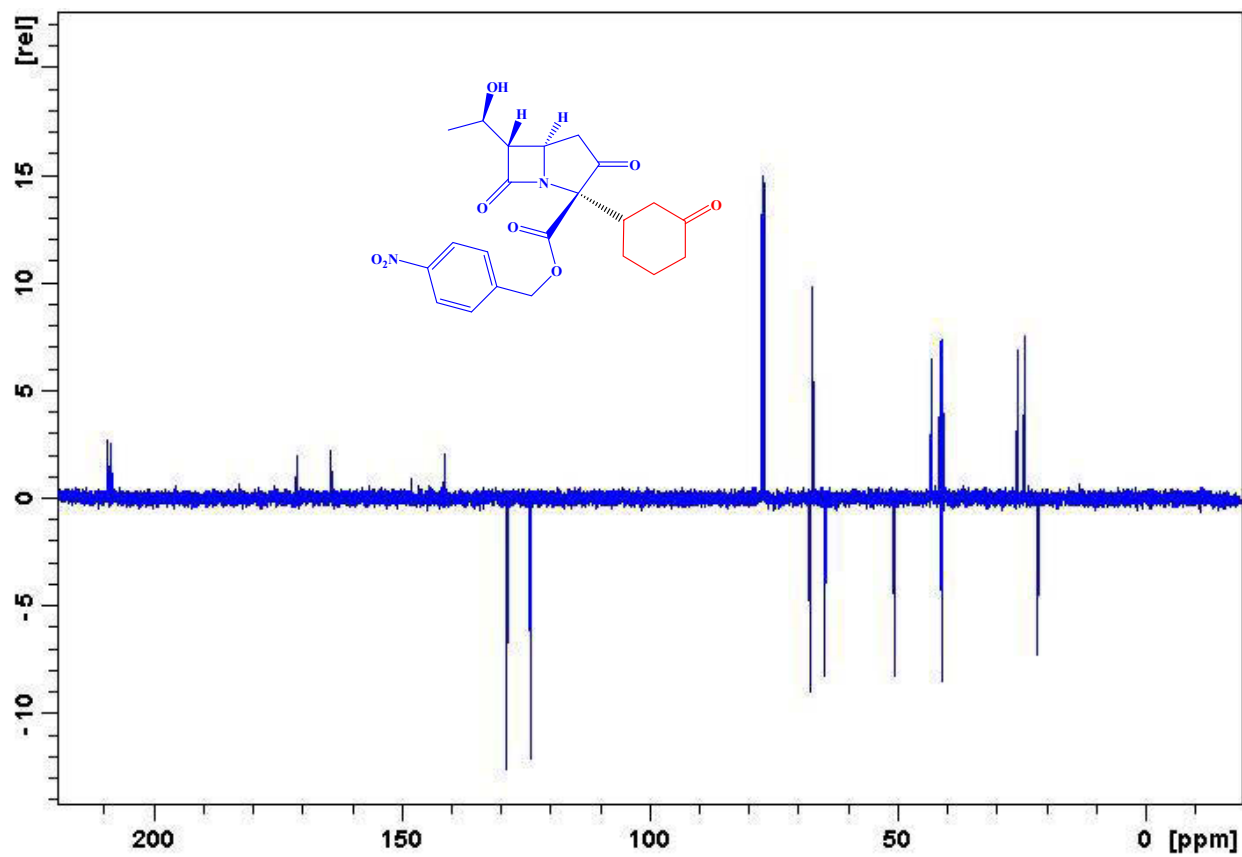
¹³C NMR for (2*S*, 5*R*, 6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxocyclopentyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5a)



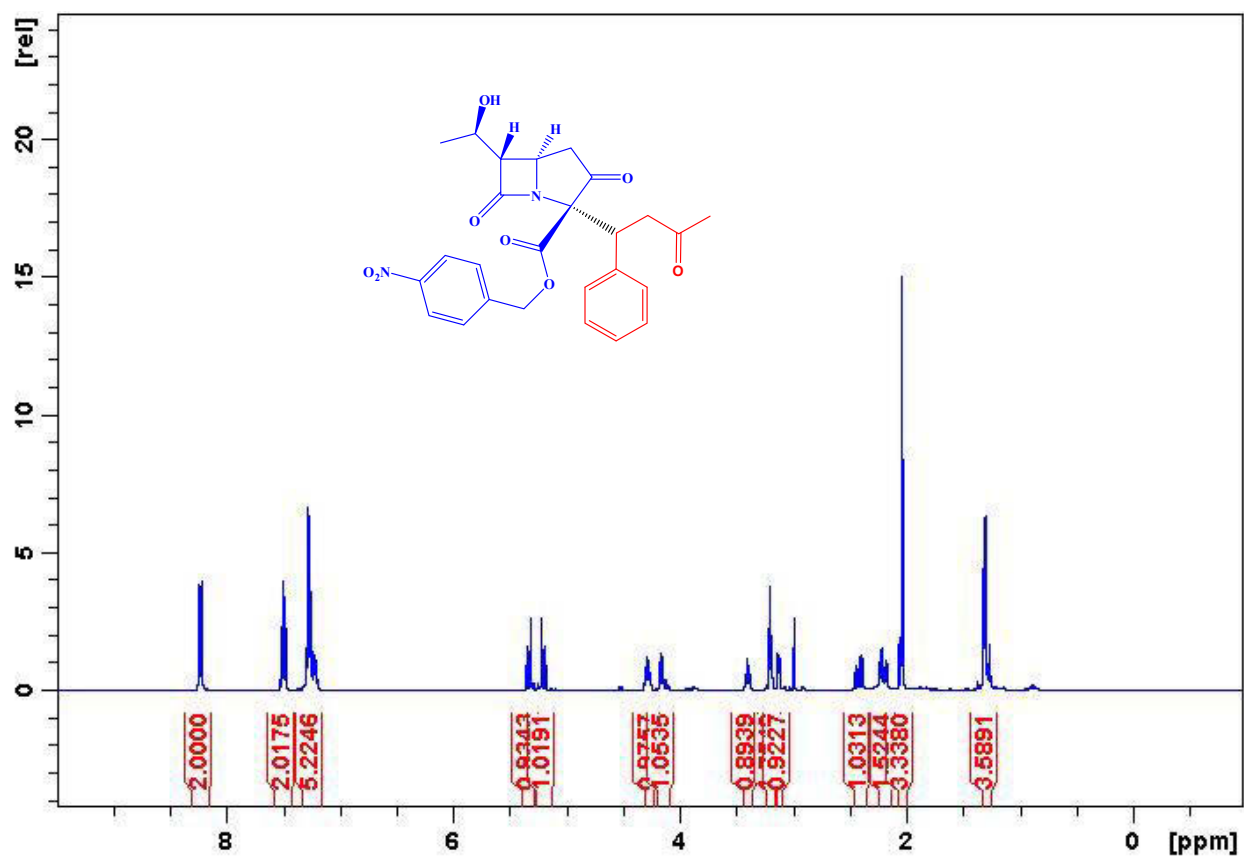
¹H NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxocyclohexyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5b)



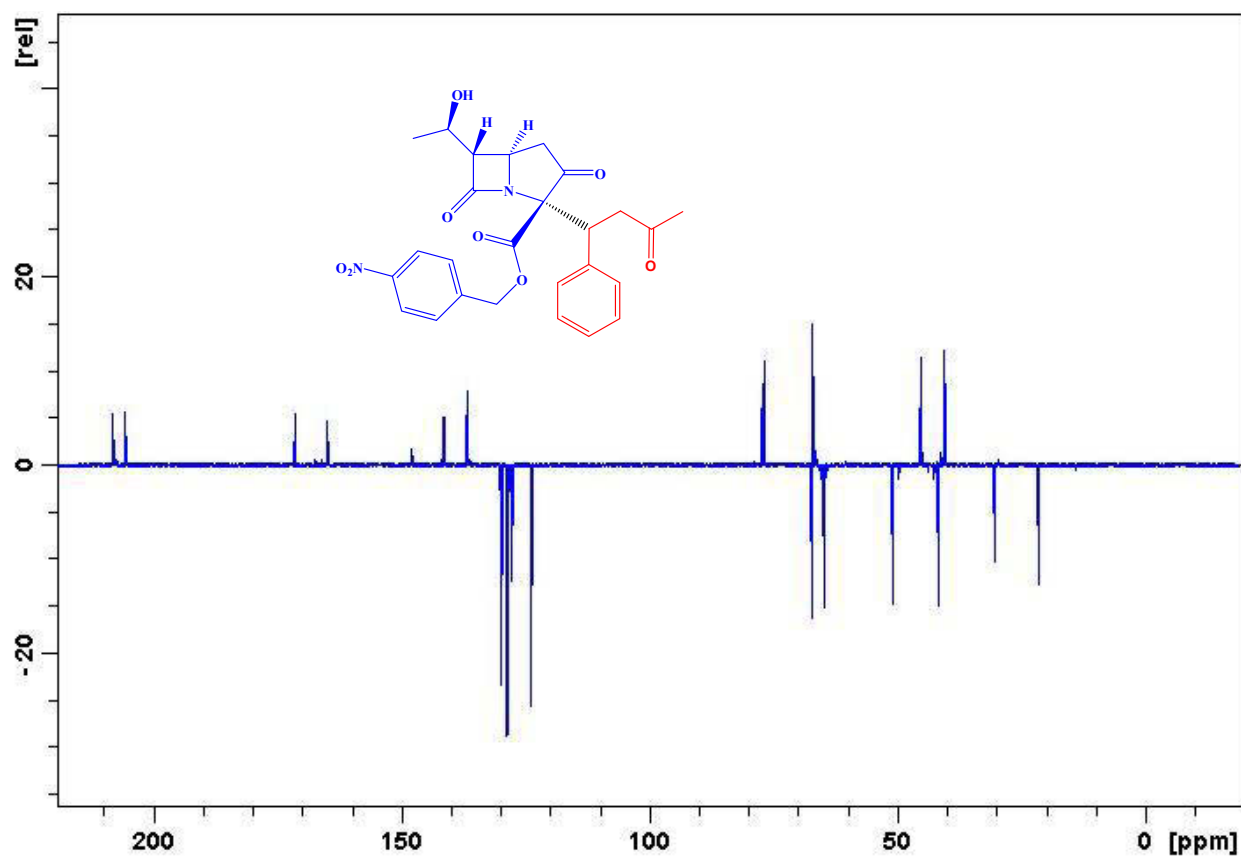
¹³C NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxocyclohexyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5b)



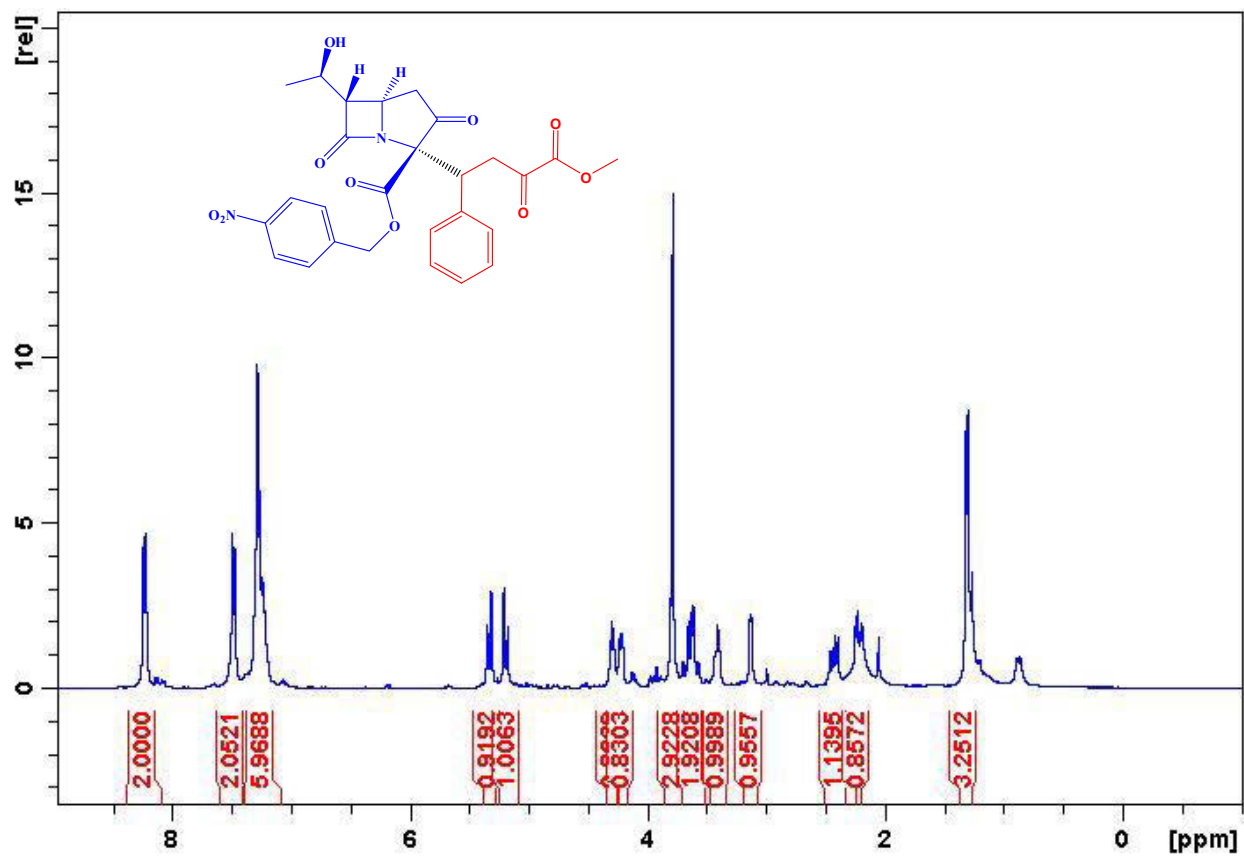
¹H NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*S*)-3-oxo-1-phenylbutyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5c)



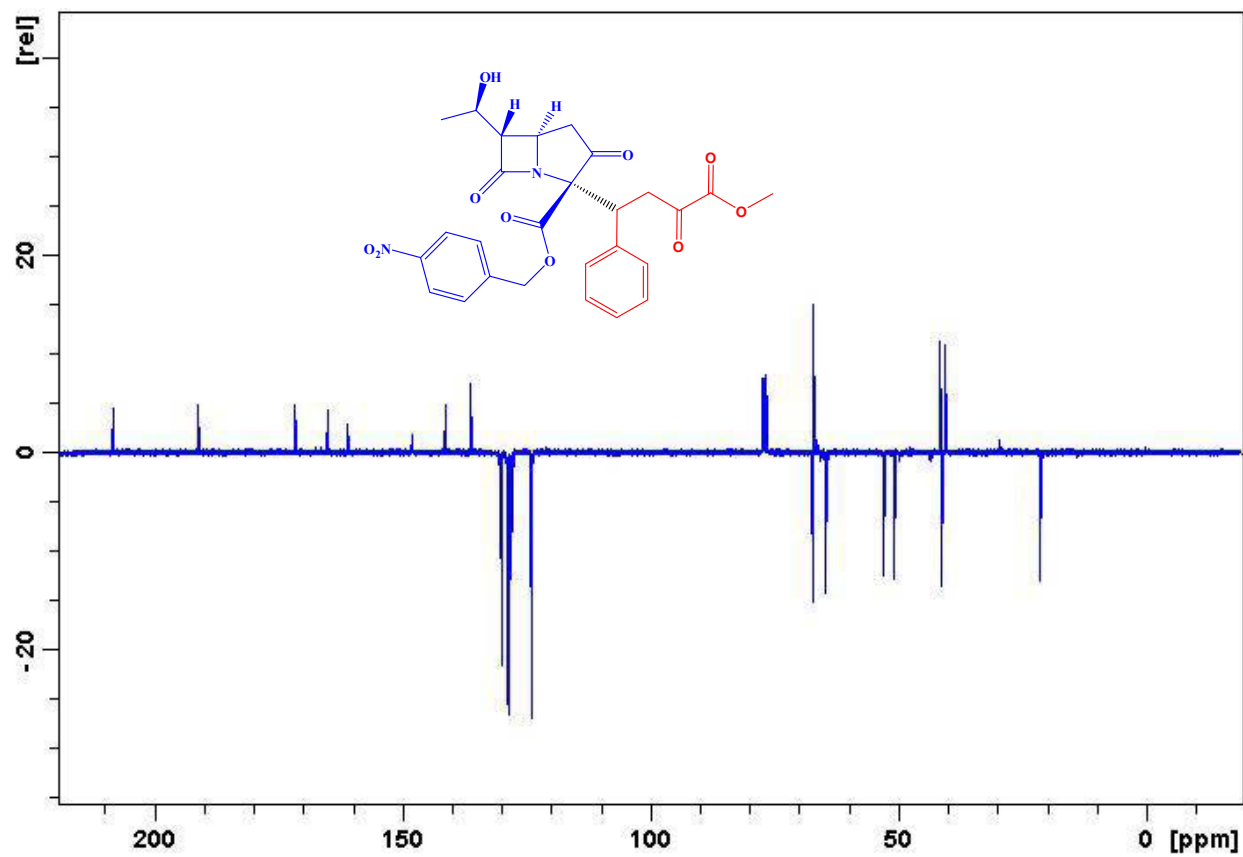
¹³C NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*S*)-3-oxo-1-phenylbutyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5c)



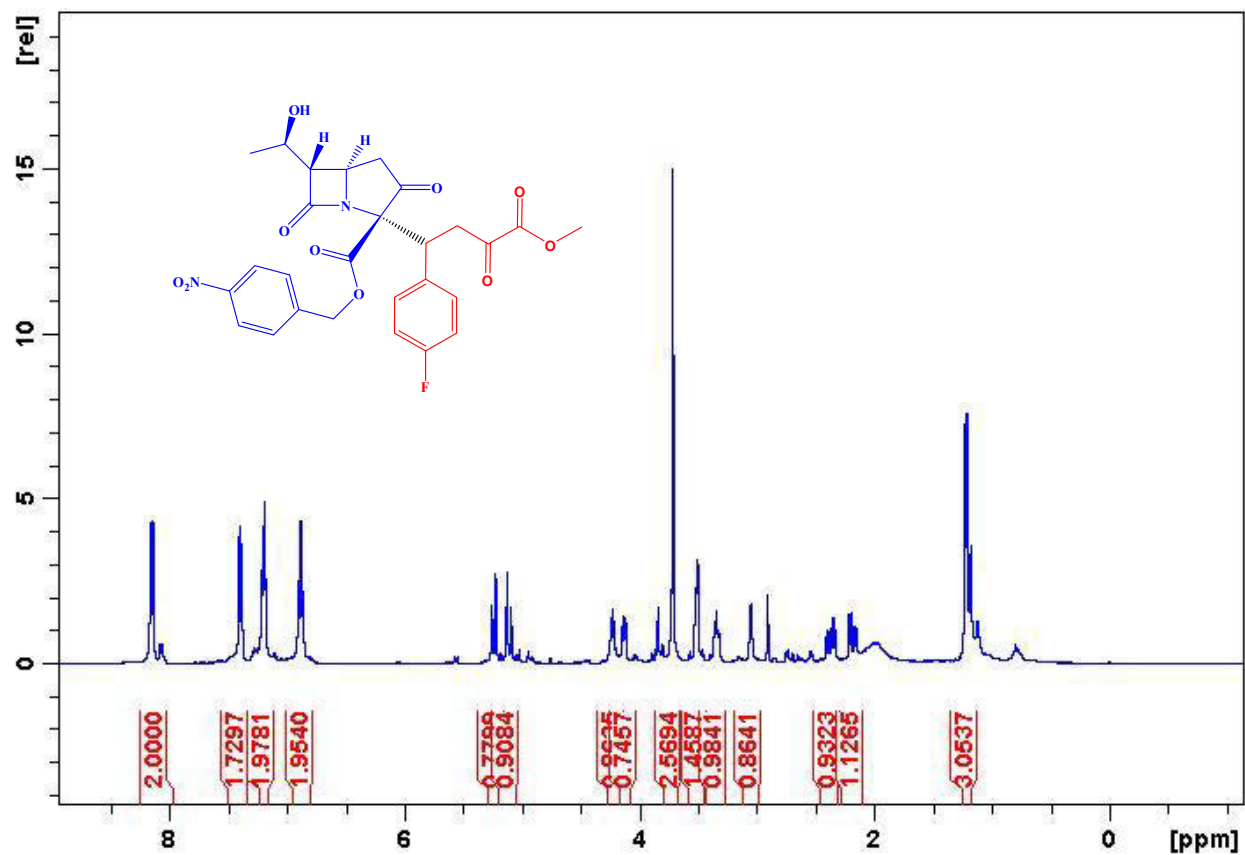
¹H NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-4-methoxy-3,4-dioxo-1-phenylbutyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5d)



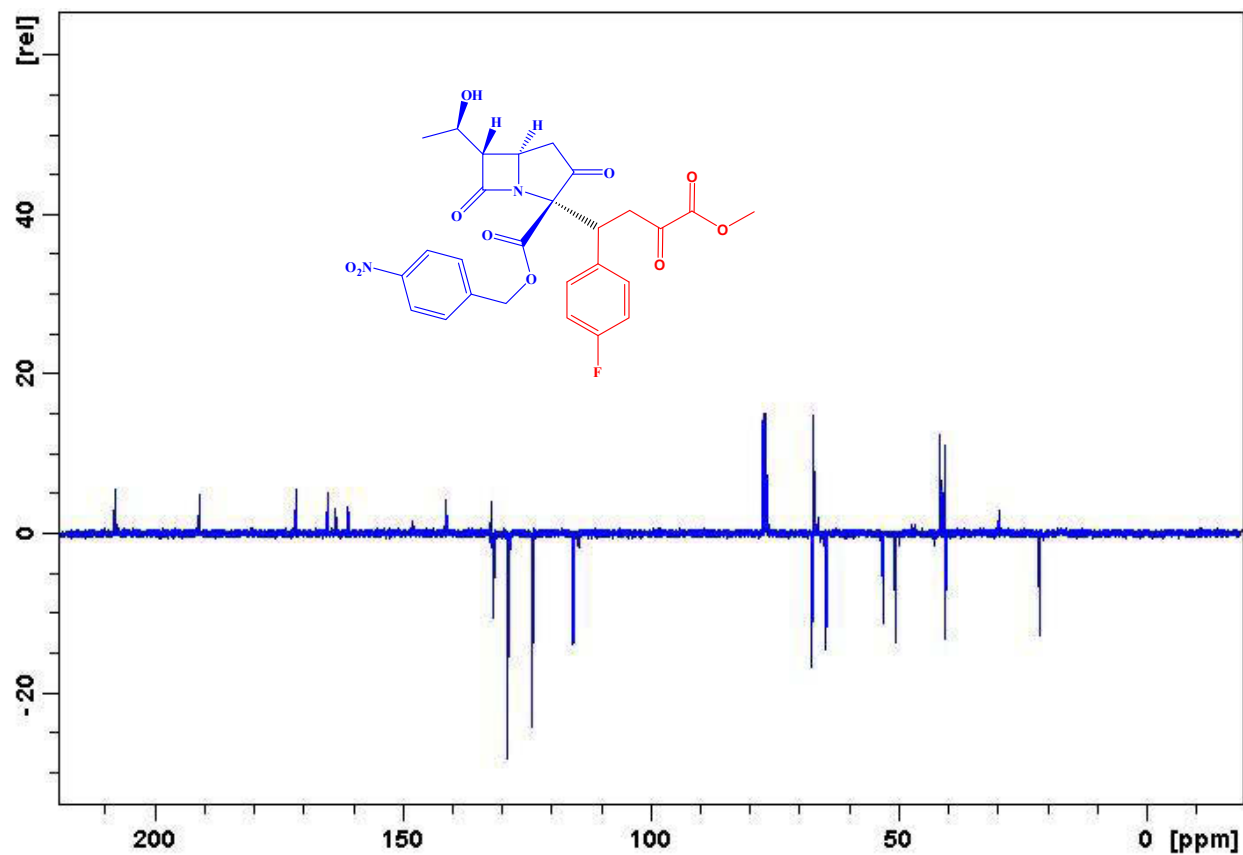
^{13}C NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-4-methoxy-3,4-dioxo-1-phenylbutyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5d)



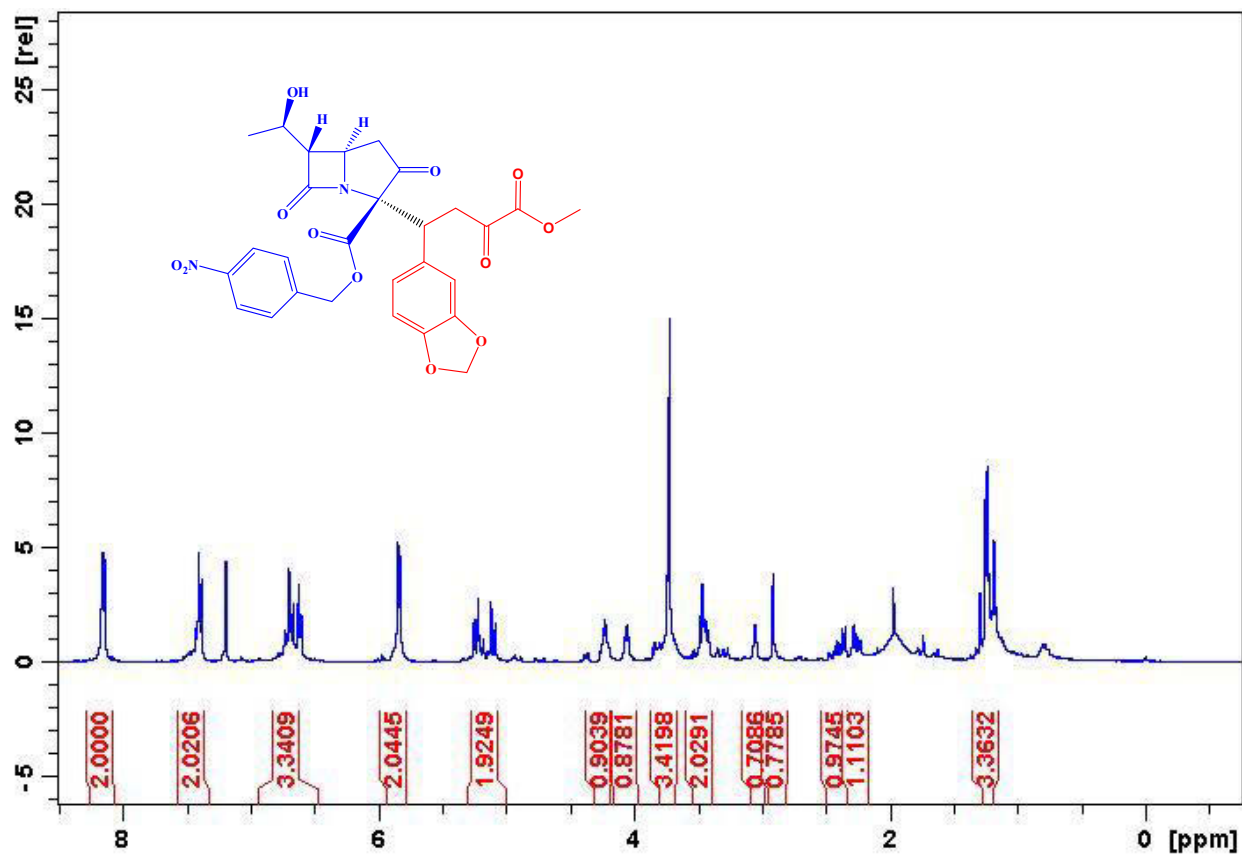
¹H NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*S*)-1-(4-fluorophenyl)-4-methoxy-3,4-dioxobutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5e)



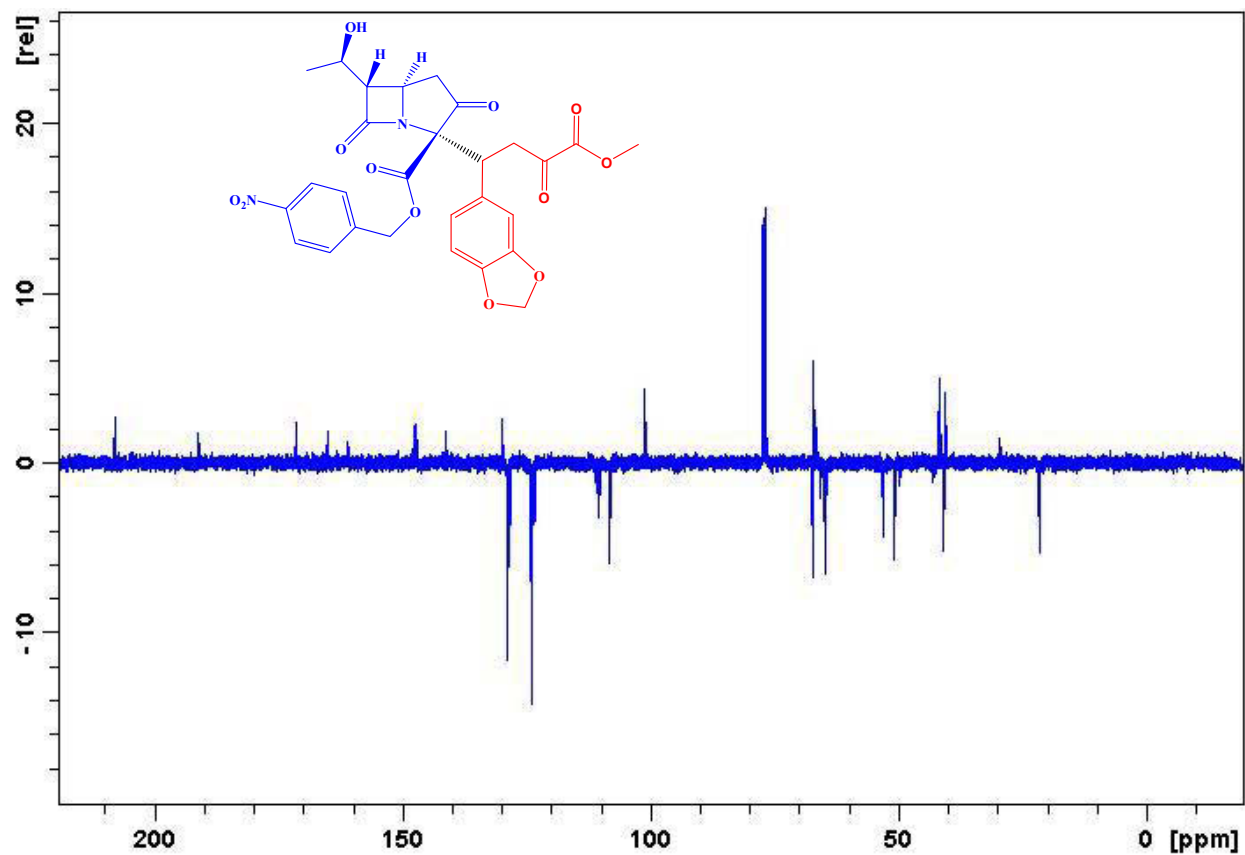
^{13}C NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*S*)-1-(4-fluorophenyl)-4-methoxy-3,4-dioxobutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5e)



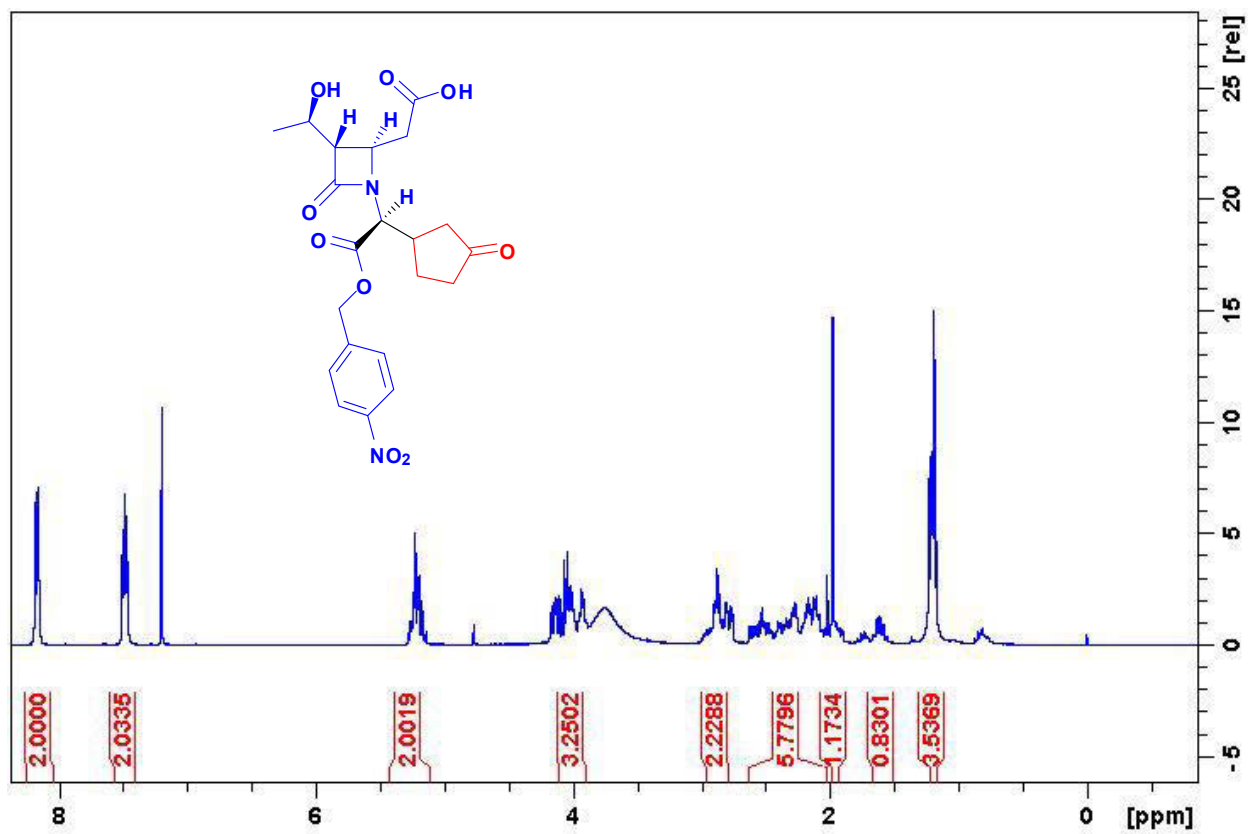
¹H NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*S*)-1-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-3,4-dioxobutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5f)



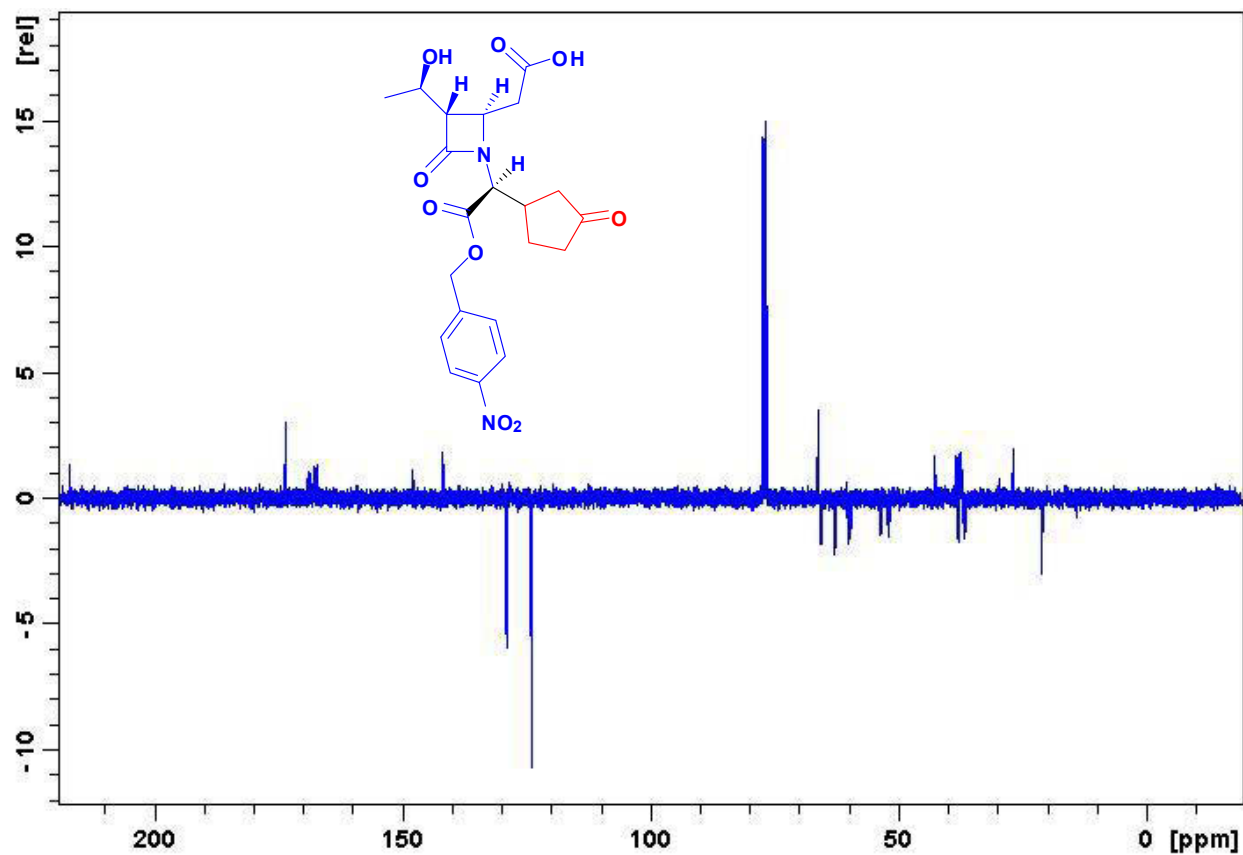
^{13}C NMR spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*S*)-1-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-3,4-dioxobutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5f)



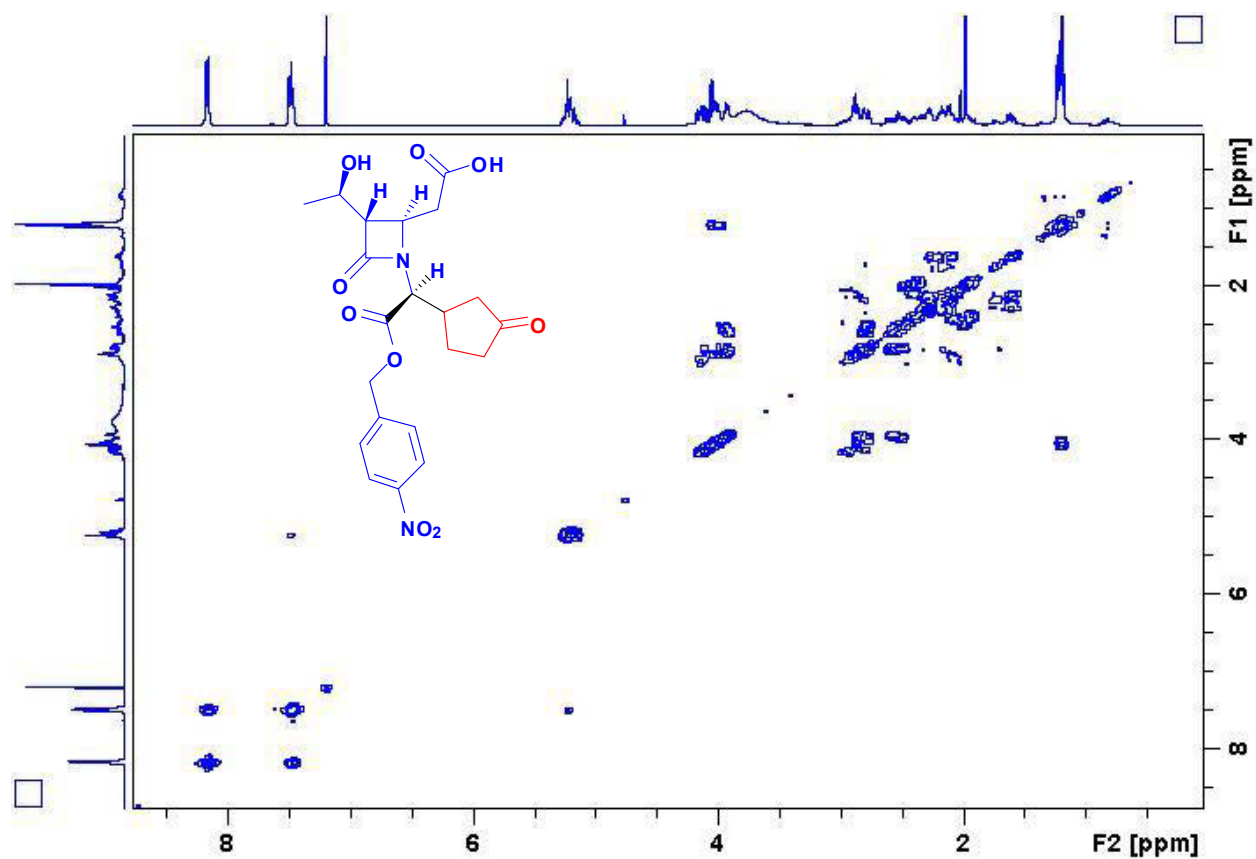
¹H NMR spectra of 2-((2R, 3S)-3-(1-Hydroxyethyl)-1-(2-(4-nitrobenzyloxy)-2-oxo-1-(3-oxocyclopentyl)ethyl)-4-oxoazetidin-2-yl) acetic acid (6)



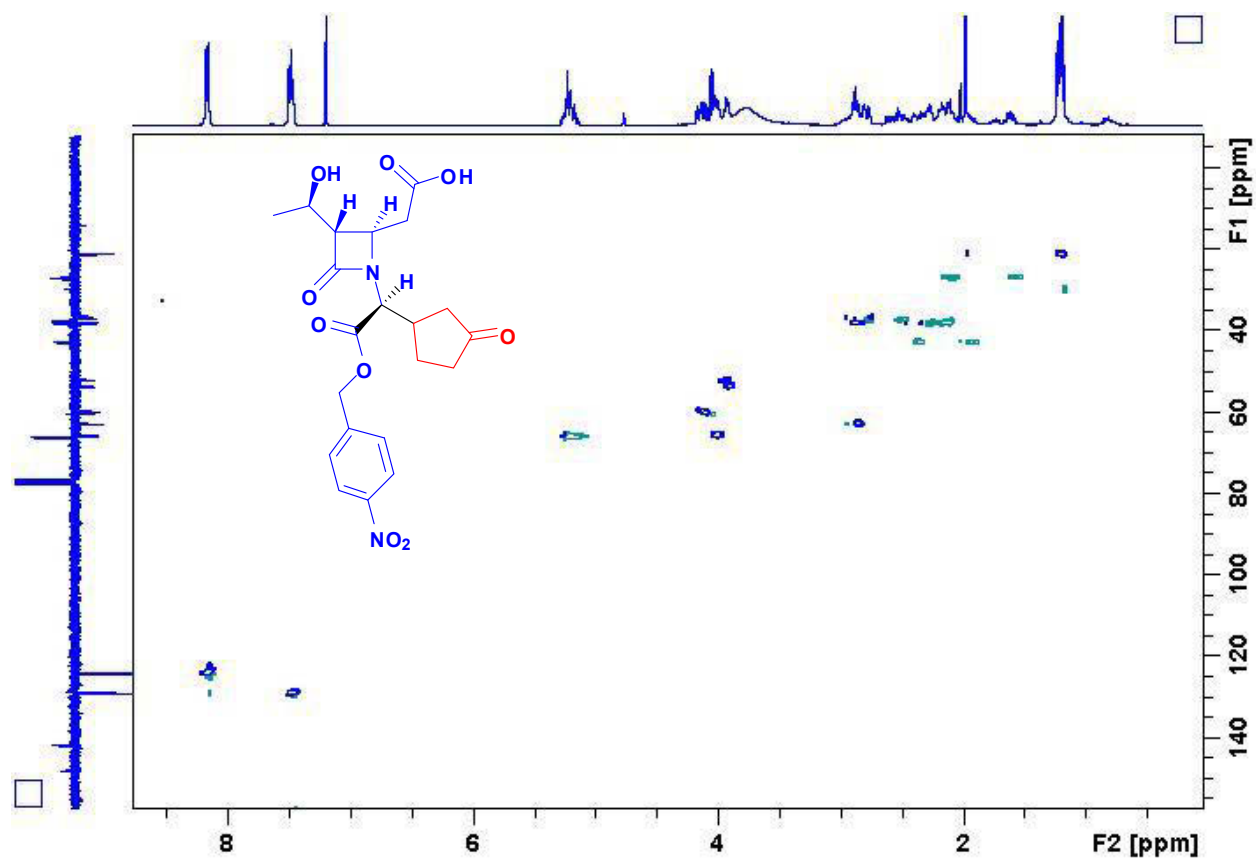
¹³C NMR spectra of 2-((2R, 3S)-3-(1-Hydroxyethyl)-1-(2-(4-nitrobenzyloxy)-2-oxo-1-(3-oxocyclopentyl)ethyl)-4-oxoazetidin-2-yl)acetic acid (6)



Cosy spectra of 2-((2R,3S)-3-(1-Hydroxyethyl)-1-(2-(4-nitrobenzyloxy)-2-oxo-1-(3-oxocyclopentyl)ethyl)-4-oxoazetidin-2-yl)acetic acid (6)



HSQC spectra of 2-((2R,3S)-3-(1-Hydroxyethyl)-1-(2-(4-nitrobenzyloxy)-2-oxo-1-(3-oxocyclopentyl)ethyl)-4-oxoazetidin-2-yl)acetic acid (6)



HMBC spectra for 2-((2R, 3S)-3-(1-Hydroxyethyl)-1-(2-(4-nitrobenzyloxy)-2-oxo-1-(3-oxocyclopentyl)ethyl)-4-oxoazetidin-2-yl)acetic acid (6)

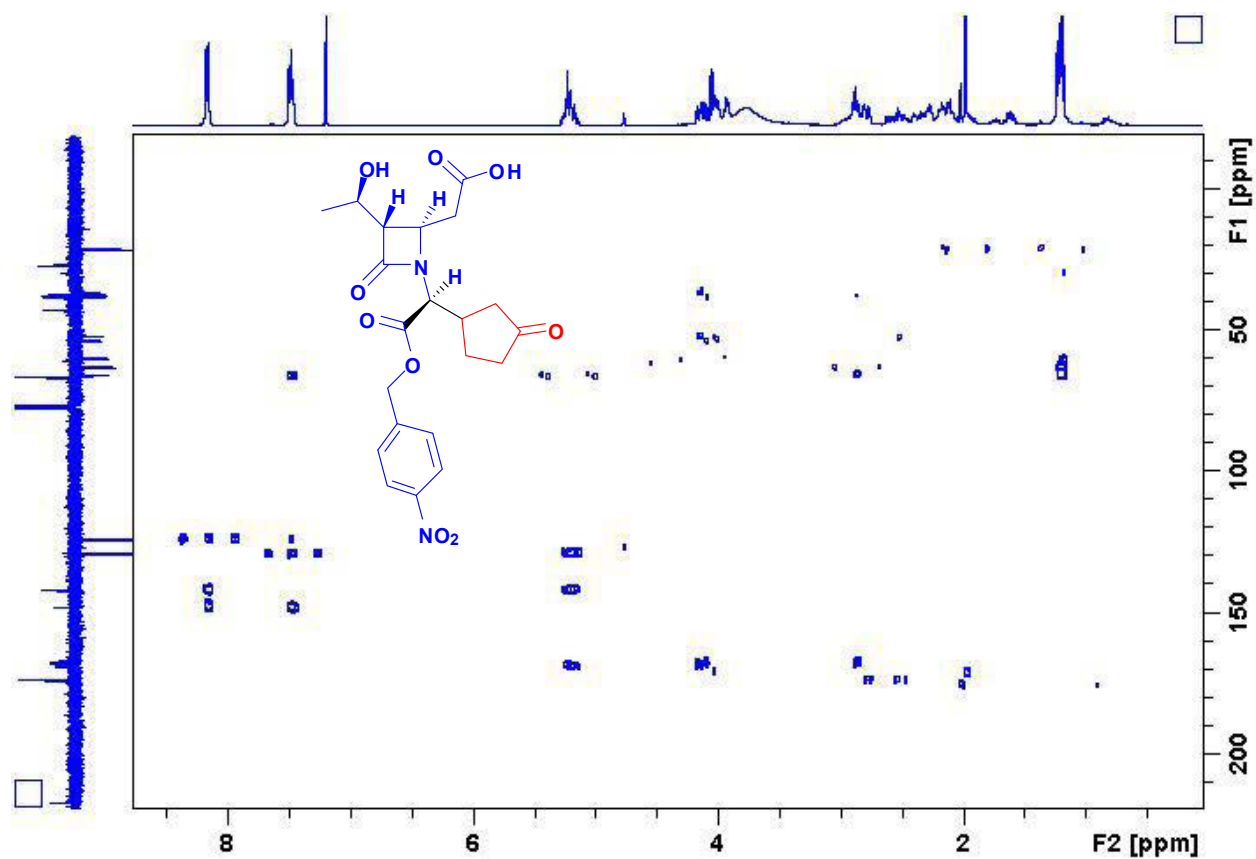


Figure 10 displays the ¹H-¹³C HMQC NMR spectrum of compound 10. The chemical structure of compound 10 is shown as an inset. The structure is a 4-nitrobenzyl 2-(4-oxocyclopentyl)-3-hydroxy-4-methyl-5-oxo-2,3-dihydro-1H-imidazole-5-carboxylate. The spectrum shows correlations between ¹H and ¹³C chemical shifts. The ¹H chemical shift (F2) ranges from 0 to 10 ppm, and the ¹³C chemical shift (F1) ranges from 0 to 100 ppm. The spectrum includes 1D ¹H and ¹³C NMR spectra as projections along the top and left axes. The 2D plot shows a series of cross-peaks, with a prominent cluster of peaks in the aromatic region (6-8 ppm ¹H, 120-150 ppm ¹³C) and another cluster in the aliphatic region (1-5 ppm ¹H, 20-60 ppm ¹³C). The inset chemical structure highlights the various functional groups and stereocenters present in the molecule.

HRMS of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-(4-methoxy phenyl)-2-nitroethyl)-3,7-dioxo-1-azabicyclo [3.2.0] heptane-2-carboxylate (3a)

Display Report

Analysis Info

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Method tune_mid.m
Sample Name st527
Comment

Acquisition Date 8/30/2013 3:17:00 PM

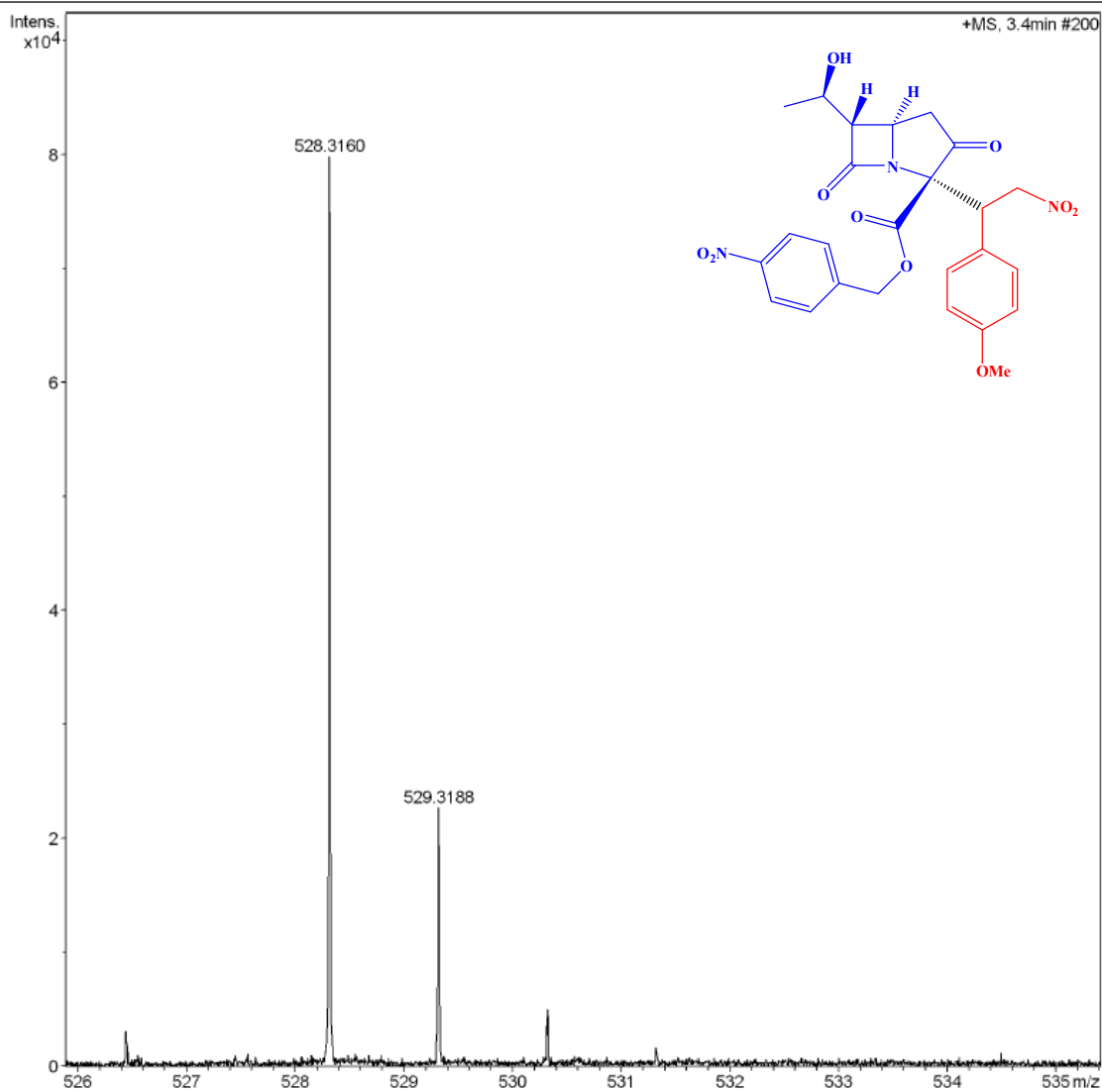
Operator BDAL@DE
Instrument maXis 21230

Acquisition Parameter

Source Type ESI
Focus Active
Scan Begin 200 m/z
Scan End 2900 m/z

Ion Polarity Positive
Set Capillary 3500 V
Set End Plate Offset -500 V
Set Collision Cell RF 2000.0 Vpp

Set Nebulizer 0.4 Bar
Set Dry Heater 180 °C
Set Dry Gas 4.0 l/min
Set Divert Valve Source



HRMS spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*R*)-2-nitro-1-phenylethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3b)

Display Report

Analysis Info

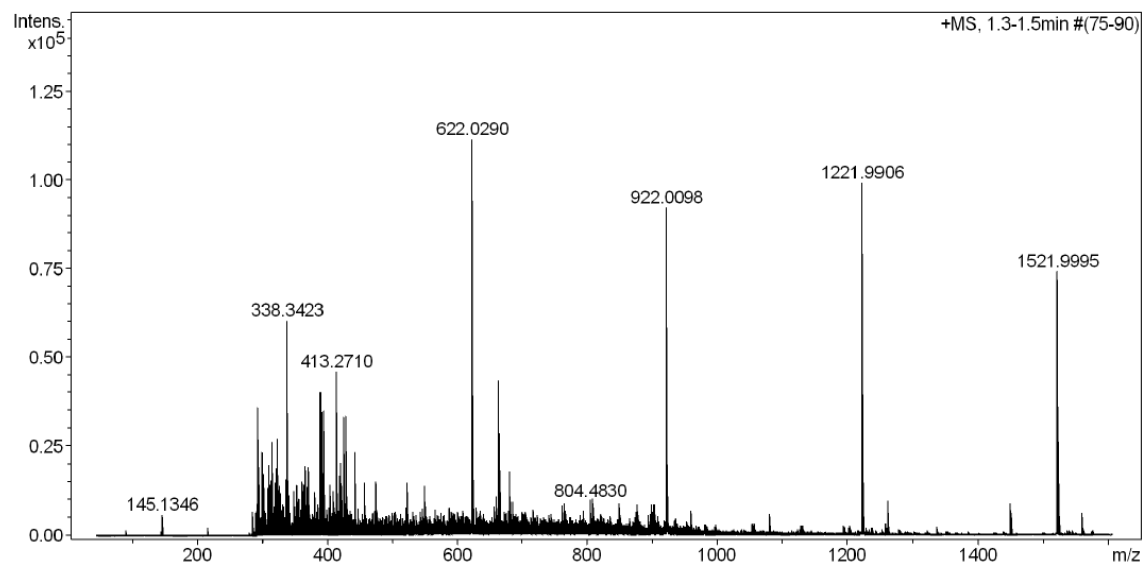
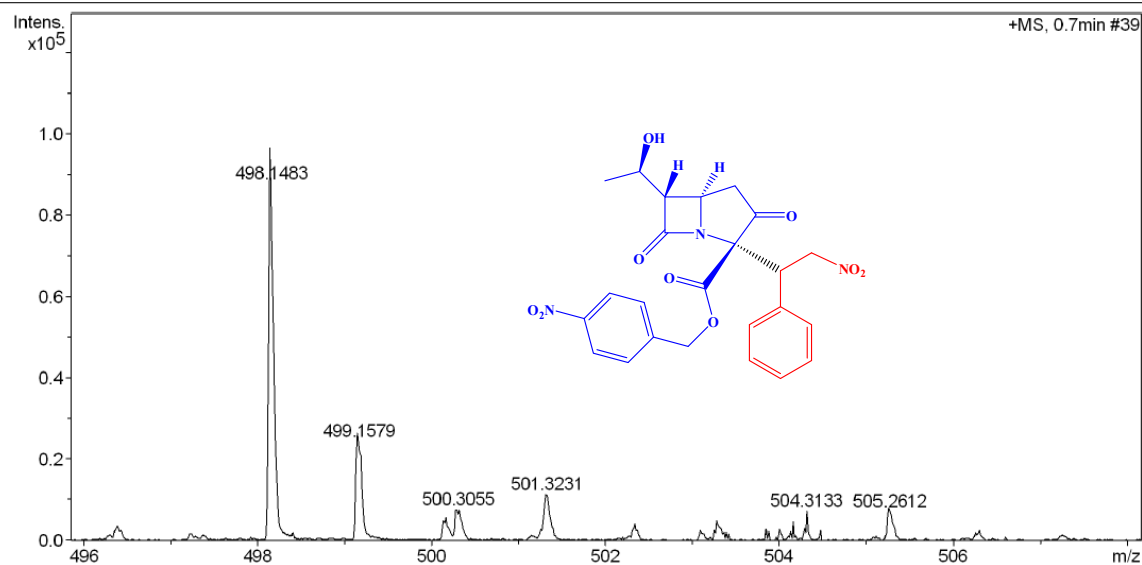
Analysis Name D:\Data\Zed\Sibo_497_1_1_01_193.d
Method fia.m
Sample Name Sib0_497_1
Comment

Acquisition Date 11/22/2013 5:39:09 PM

Operator BDAL@DE
Instrument micrOTOF-Q 10139

Acquisition Parameter

| | | | | | |
|-------------|----------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 0.4 Bar |
| Focus | Active | Set Capillary | 4500 V | Set Dry Heater | 220 °C |
| Scan Begin | 50 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 6.0 l/min |
| Scan End | 1600 m/z | Set Collision Cell RF | 600.0 Vpp | Set Divert Valve | Source |



HRMS spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*R*)-1-(4-chlorophenyl)-2-nitroethyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (3c)

Display Report

Analysis Info

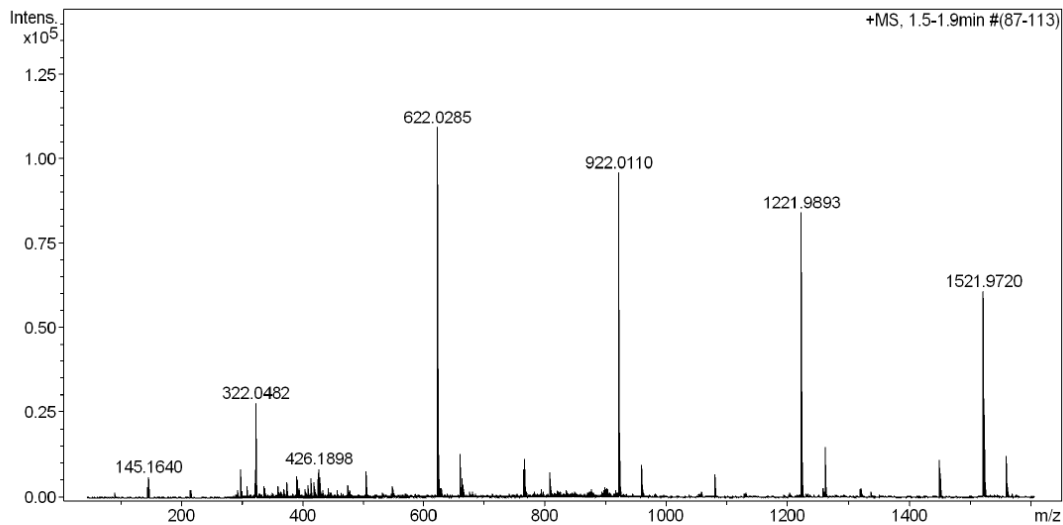
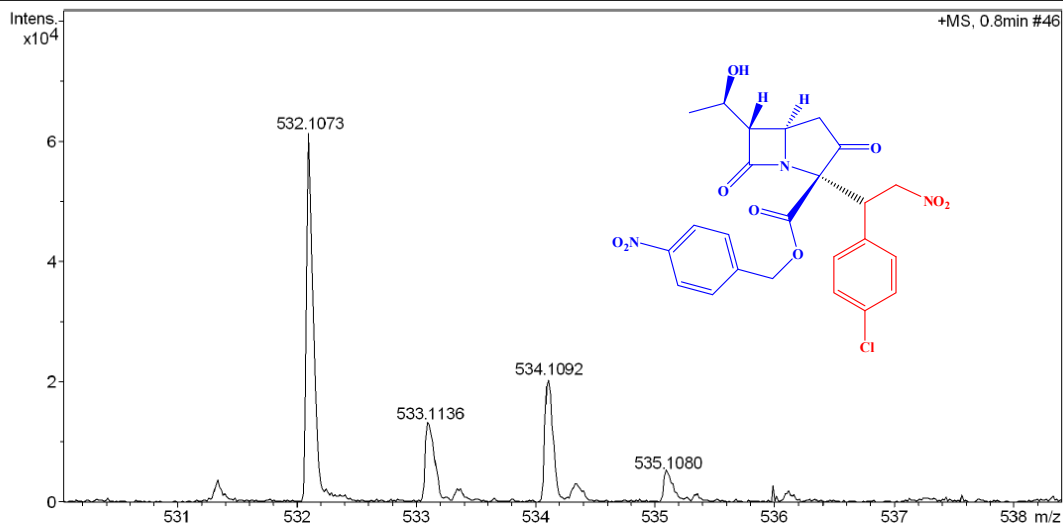
Analysis Name D:\Data\Zed\Sibo_531_1_01_190.d
 Method fia.m
 Sample Name Sib0_531
 Comment

Acquisition Date 11/22/2013 5:19:52 PM

Operator BDAL@DE
 Instrument micrOTOF-Q 10139

Acquisition Parameter

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|-------------|----------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 0.4 Bar |
| Focus | Active | Set Capillary | 4500 V | Set Dry Heater | 220 °C |
| Scan Begin | 50 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 6.0 l/min |
| Scan End | 1600 m/z | Set Collision Cell RF | 600.0 Vpp | Set Divert Valve | Source |



HRMS of (2*S*,5*R*,6*S*)-4-nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxoclopentyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5a)

Display Report

Analysis Info

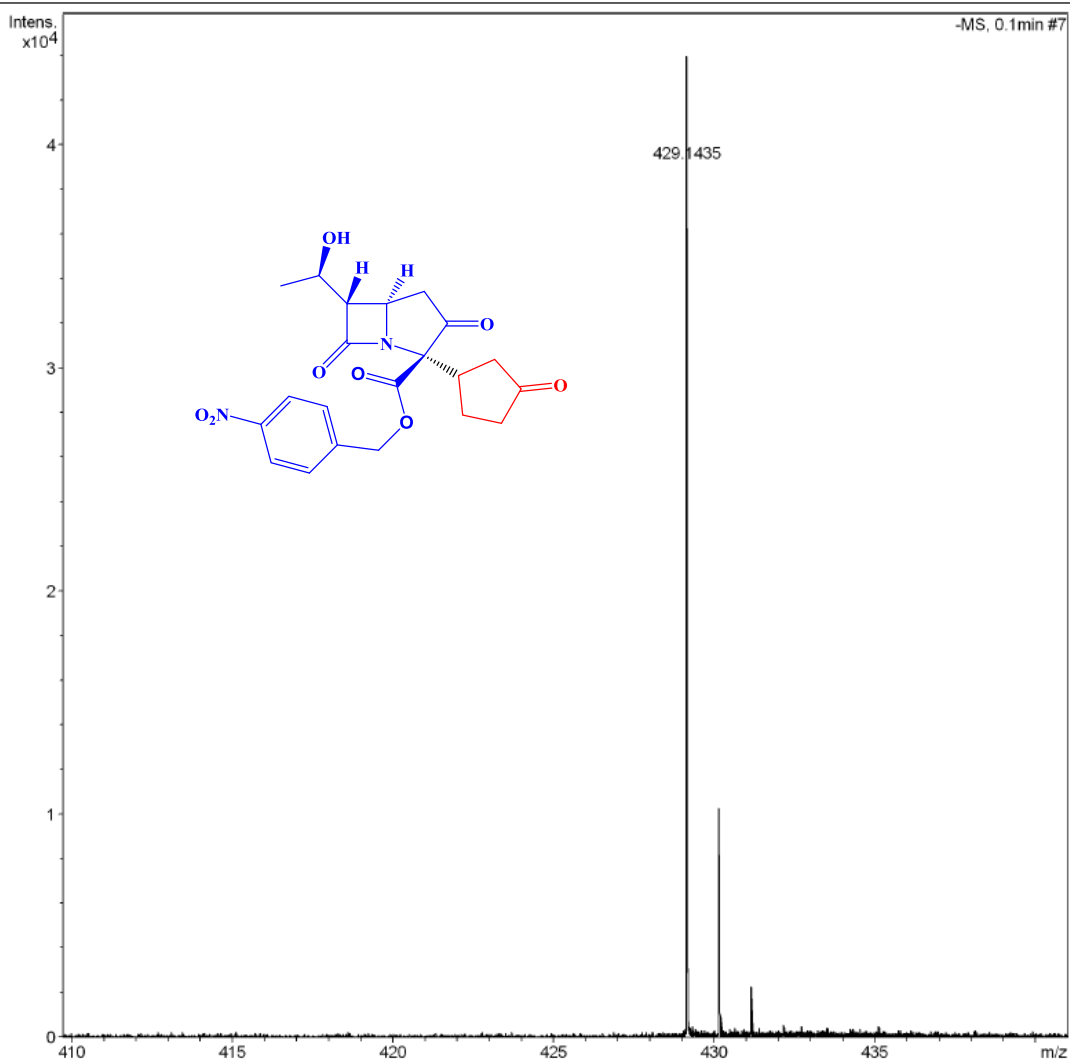
Analysis Name D:\Data\sibusiso\430000001.d
Method tune_mid.m
Sample Name 430
Comment

Acquisition Date 8/30/2013 4:23:05 PM

Operator BDAL@DE
Instrument maXis 21230

Acquisition Parameter

| | | | | | |
|-------------|----------|-----------------------|------------|------------------|-----------|
| Source Type | ESI | Ion Polarity | Negative | Set Nebulizer | 0.4 Bar |
| Focus | Active | Set Capillary | 2400 V | Set Dry Heater | 180 °C |
| Scan Begin | 200 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 4.0 l/min |
| Scan End | 2900 m/z | Set Collision Cell RF | 2000.0 Vpp | Set Divert Valve | Source |



HRMS spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-3,7-dioxo-2-((*R*)-3-oxocyclohexyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate (5b)

Display Report

Analysis Info

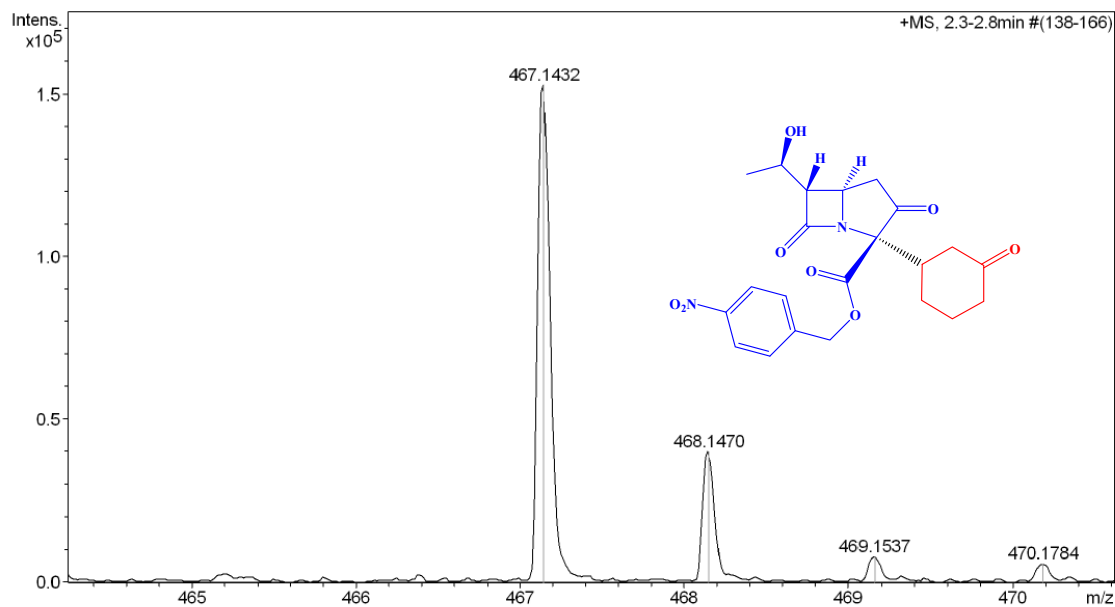
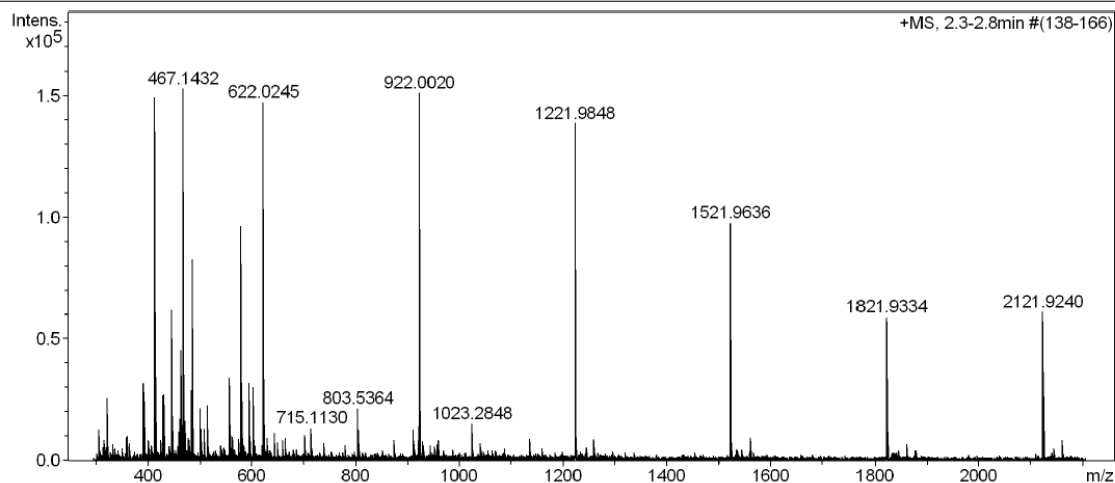
Analysis Name D:\Data\SIBUSISO\SIBUSISO 444 pos 8 feb 14000003.d
 Method tune_wide_300.m
 Sample Name SIBUSISO 444 ESI+ 8 feb 14
 Comment

Acquisition Date 2/8/2014 12:39:43 PM

Operator BDAL@DE
 Instrument micrOTOF-Q 10139

Acquisition Parameter

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|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 0.4 Bar |
| Focus | Not active | Set Capillary | 4500 V | Set Dry Heater | 200 °C |
| Scan Begin | 300 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 5.0 l/min |
| Scan End | 2200 m/z | Set Collision Cell RF | 600.0 Vpp | Set Divert Valve | Source |



HRMS spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-4-methoxy-3,4-dioxo-1-phenylbutyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5c)

Display Report

Analysis Info

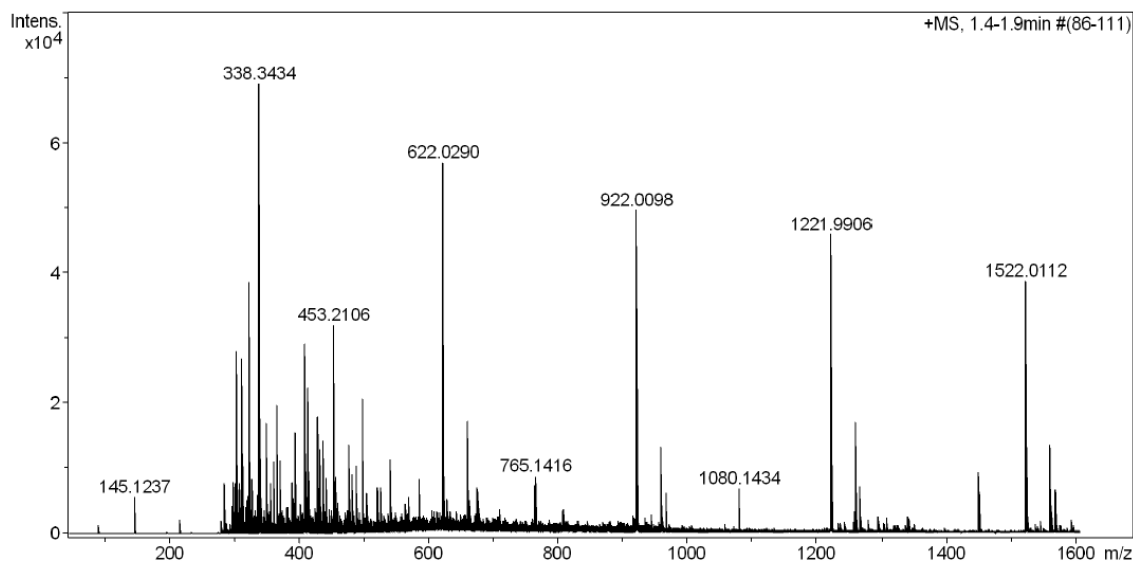
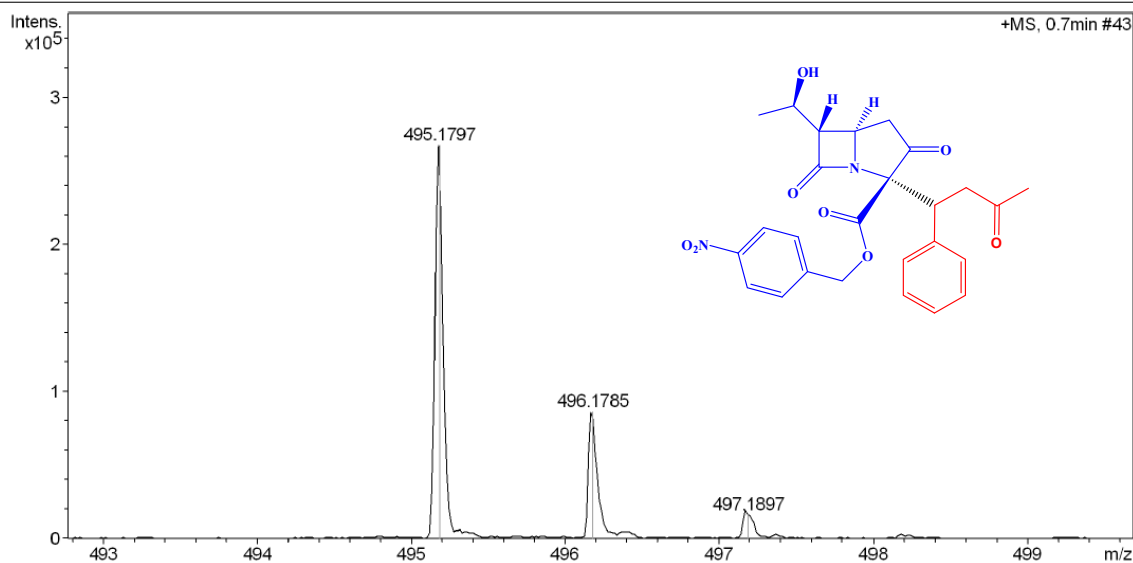
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 Method fia.m
 Sample Name Sib0_494
 Comment

Acquisition Date 11/22/2013 5:28:32 PM

Operator BDAL@DE
 Instrument micrOTOF-Q 10139

Acquisition Parameter

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|-------------|----------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 0.4 Bar |
| Focus | Active | Set Capillary | 4500 V | Set Dry Heater | 220 °C |
| Scan Begin | 50 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 6.0 l/min |
| Scan End | 1600 m/z | Set Collision Cell RF | 600.0 Vpp | Set Divert Valve | Source |



HRMS spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 6-((*R*)-1-hydroxyethyl)-2-((*S*)-4-methoxy-3,4-dioxo-1-phenylbutyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5d)

Display Report

Analysis Info

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 Method fia.m
 Sample Name Sib0_538
 Comment

Acquisition Date 11/22/2013 5:50:27 PM

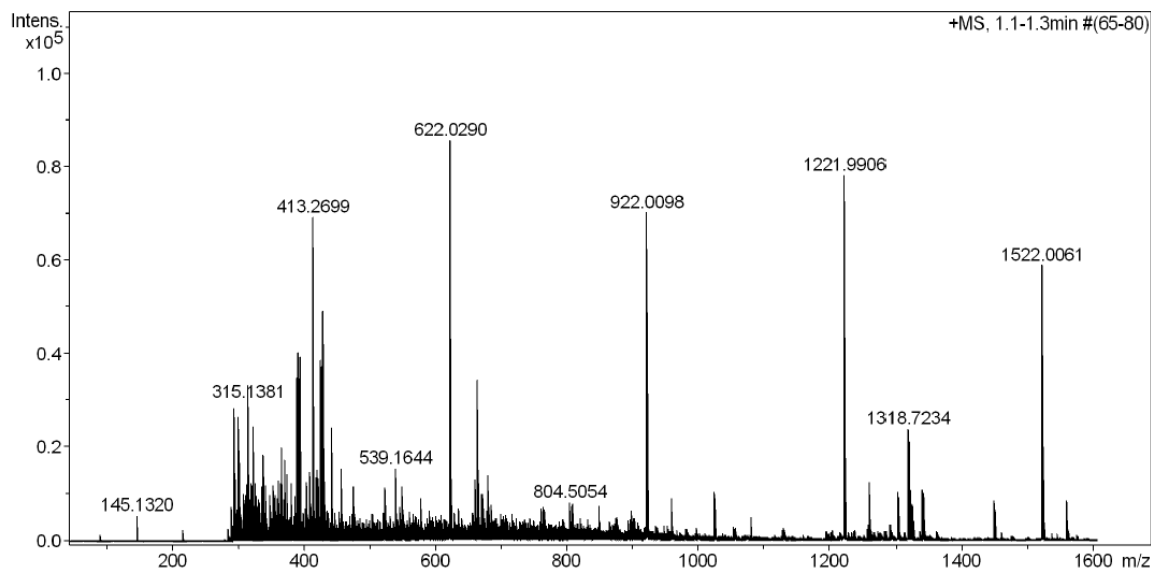
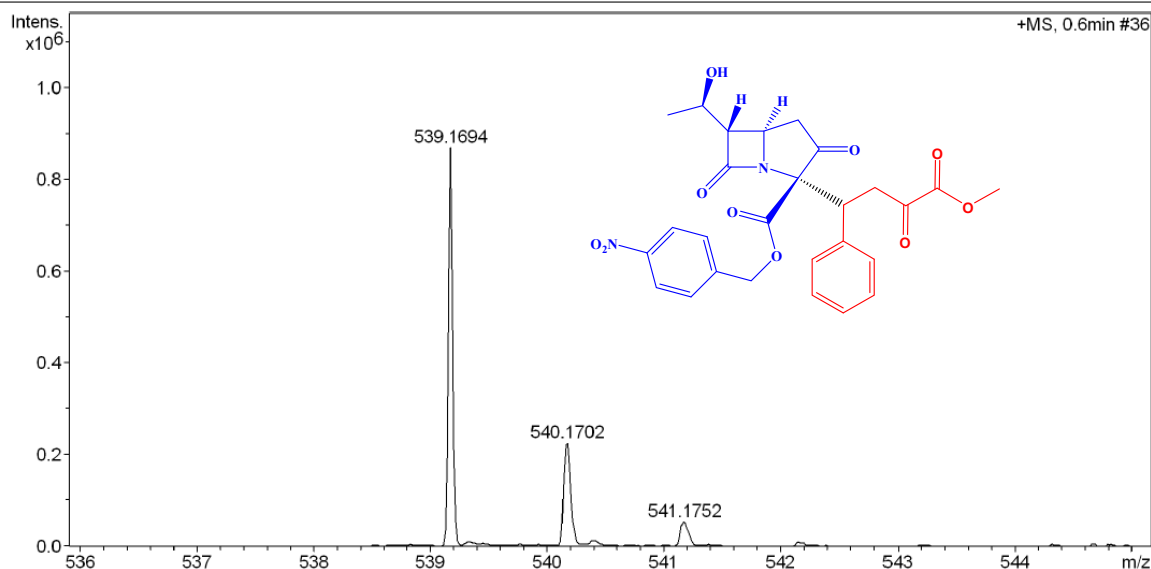
Operator BDAL@DE
 Instrument micrOTOF-Q 10139

Acquisition Parameter

Source Type ESI
 Focus Active
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 Scan End 1600 m/z

Ion Polarity Positive
 Set Capillary 4500 V
 Set End Plate Offset -500 V
 Set Collision Cell RF 600.0 Vpp

Set Nebulizer 0.4 Bar
 Set Dry Heater 220 °C
 Set Dry Gas 6.0 l/min
 Set Divert Valve Source



(2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*S*)-1-(4-fluorophenyl)-4-methoxy-3,4-dioxobutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5e)

Display Report

Analysis Info

Analysis Name D:\Data\SIBUSISO\SIBUSISO 444+ 8 feb 14000001.d
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 Sample Name SIBUSISO 444+ 8 feb 14
 Comment

Acquisition Date 2/8/2014 12:15:05 PM

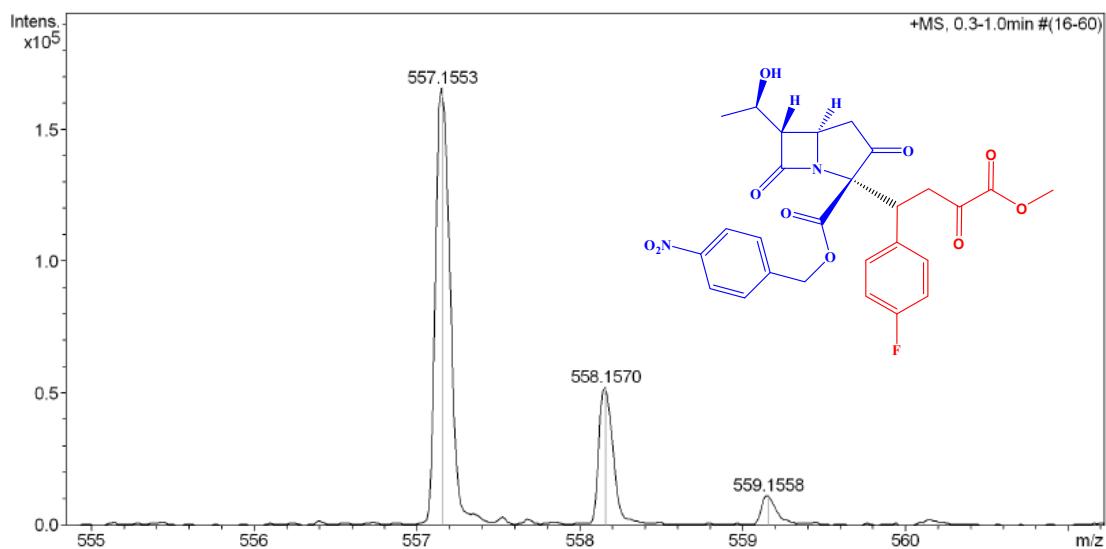
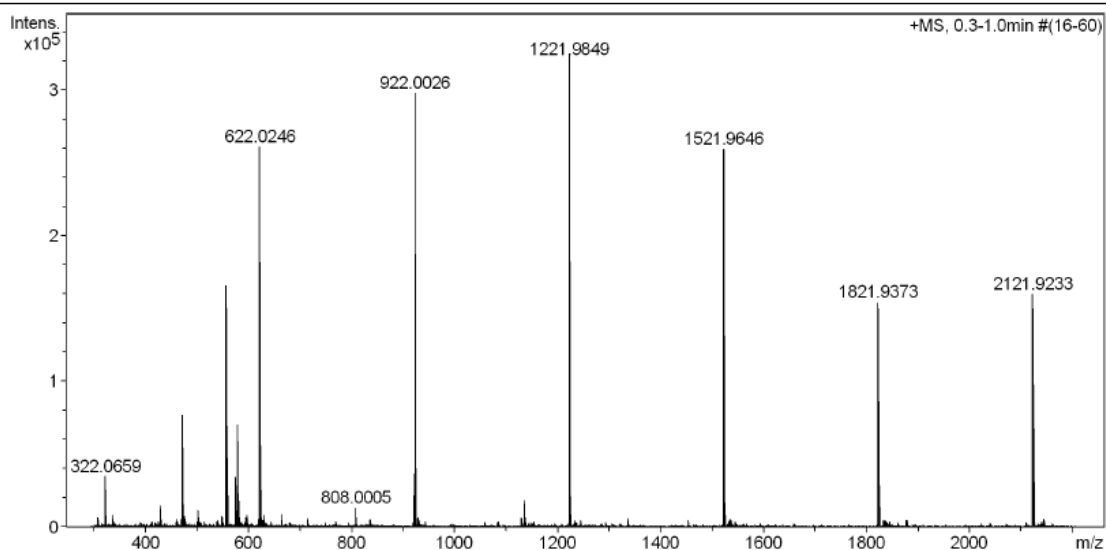
Operator BDAL@DE
 Instrument micrOTOF-Q 10139

Acquisition Parameter

Source Type ESI
 Focus Not active
 Scan Begin 300 m/z
 Scan End 2200 m/z

Ion Polarity Positive
 Set Capillary 4500 V
 Set End Plate Offset -500 V
 Set Collision Cell RF 600.0 Vpp

Set Nebulizer 0.4 Bar
 Set Dry Heater 200 °C
 Set Dry Gas 5.0 l/min
 Set Divert Valve Source



HRSM spectra of (2*S*,5*R*,6*S*)-4-Nitrobenzyl 2-((*S*)-1-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-3,4-dioxobutyl)-6-((*R*)-1-hydroxyethyl)-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (5f)

Display Report

Analysis Info

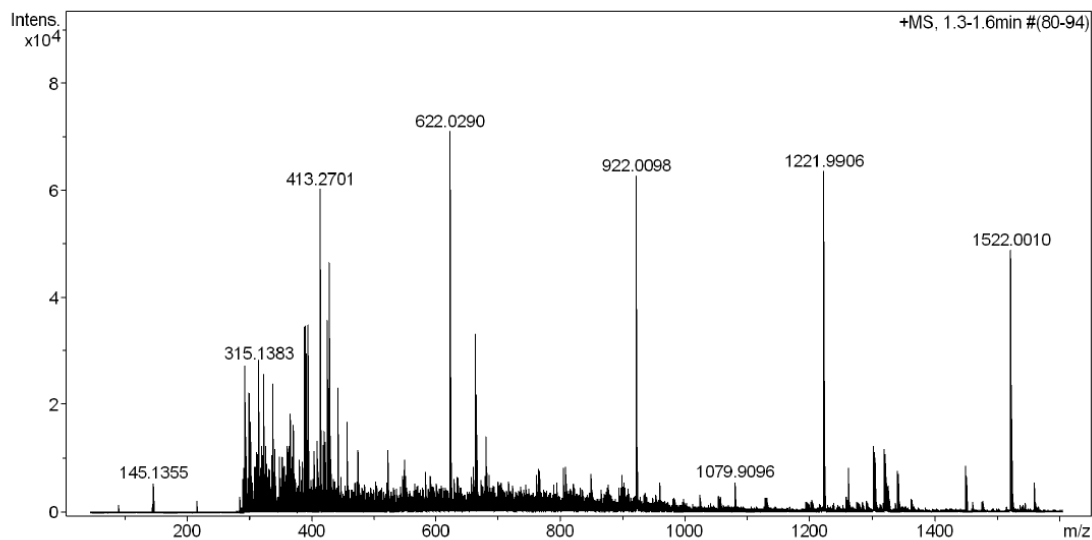
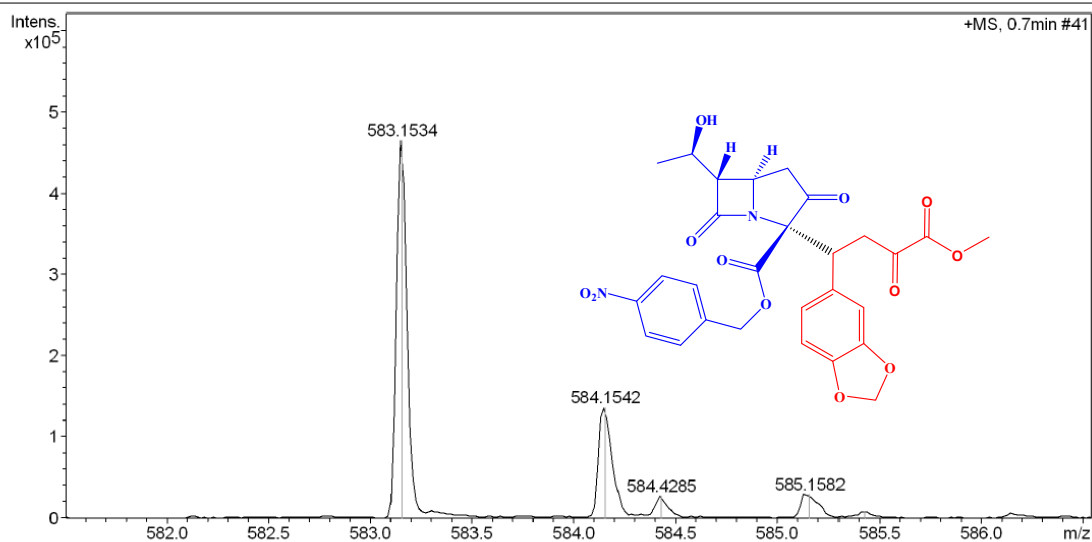
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Method fia.m
Sample Name Sibo_582
Comment

Acquisition Date 11/22/2013 5:53:39 PM

Operator BDAL@DE
Instrument micrOTOF-Q 10139

Acquisition Parameter

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|-------------|----------|-----------------------|-----------|------------------|-----------|
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| Focus | Active | Set Capillary | 4500 V | Set Dry Heater | 220 °C |
| Scan Begin | 50 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 6.0 l/min |
| Scan End | 1600 m/z | Set Collision Cell RF | 600.0 Vpp | Set Divert Valve | Source |



HRMS spectra of 2-((2*R*,3*S*)-3-(1-Hydroxyethyl)-1-(2-(4-nitrobenzyloxy)-2-oxo-1-(3-oxocyclopentyl)ethyl)-4-oxoazetidin-2-yl)acetic acid (6)

Display Report

Analysis Info

Analysis Name D:\Data\SIBUSISO\SIBUSISO 448 neg 8 feb 14000002.d
 Method tune_wide_300.m
 Sample Name SIBUSISO 448 NEGATIVE 8 feb 14
 Comment

Acquisition Date 2/8/2014 1:06:46 PM

Operator BDAL@DE
 Instrument micrOTOF-Q 10139

Acquisition Parameter

| | | | | | |
|-------------|------------|-----------------------|-----------|------------------|-----------|
| Source Type | ESI | Ion Polarity | Negative | Set Nebulizer | 0.4 Bar |
| Focus | Not active | Set Capillary | 3500 V | Set Dry Heater | 200 °C |
| Scan Begin | 300 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 5.0 l/min |
| Scan End | 2200 m/z | Set Collision Cell RF | 600.0 Vpp | Set Divert Valve | Source |

